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(54) **Diaminotrifluoromethylpyrimidine derivatives, process for their production and phospholipase A2 inhibitor containing them.**

(57) A diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:

(I)

wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y is alkyl, $-CW^3R^6$, $-COCOR^7$, $-NHCOR^7$, $-C(=W^3)W^4R^8$, $-(NH)_mSO_2R^9$, $-(NH)_mSO_2OR^{10}$ or $-(NH)_mSO_2N(R^{11})R^{12}$, wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which

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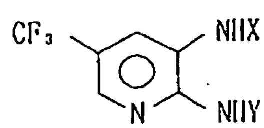
may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded.

The present invention relates to novel diaminotrifluoromethylpyridine derivatives or their salts, a process for their production, a phospholipase A_2 inhibitor, an anti-inflammatory agent and an anti-pancreatitis agent containing them, and novel trifluoromethylpyridine derivatives as intermediates.

As a diaminotrifluoromethylpyridine derivative, for example, U.S. Patents 3,746,531 and 3,962,263 disclose a pyridine as an active ingredient of a herbicide, which has trifluoromethyl at the 5-position, -NHCO-CF_2-T^1 wherein T^1 is a hydrogen atom, a chlorine atom, a fluorine atom, alkyl or haloalkyl at either the 2-position or the 3-position, and -NHCO-CF_2-T^2 wherein T^2 is a hydrogen atom, a chlorine atom, a fluorine atom, alkyl, haloalkyl or alkylcarbonyl, or -NHCOOT^3 wherein T^3 is C_{1-4} lower alkyl or phenyl at the other position. However, this is different in the chemical structure from the diaminotrifluoromethylpyridine derivative of the present invention. Further, U.S. Patent 3,961,063 discloses a trifluoromethyl-substituted pyridine as an active ingredient of an anthelmintic, which has -NHCSNHCOT^4 wherein T^4 is alkoxy, at the 2- and 3-positions. However, this compound is different in the chemical structure from the diaminotrifluoromethylpyridine derivative of the present invention.

The present invention provides a diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:



(I)

wherein X is -CW^1R^1, -$COCOR^2$, -CW^1NHCOR^2, -$C(=W^1)W^2R^3$ or -$CW^1N(R^4)R^5$, and Y is alkyl, -CW^3R^6, -$COCOR^7$, -$NHCOR^7$, -$C(=W^3)W^4R^8$, -$(NH)_mSO_2R^9$, -$(NH)_mSO_2OR^{10}$ or -$(NH)_mSO_2N(R^{11})R^{12}$, wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is -$COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is -$COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or -$COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded; a process for its production; a phospholipase A_2 inhibitor, an anti-inflammatory agent and an anti-pancreatitis agent containing it, and a trifluoromethylpyridine derivative as an intermediate.

Now, the present invention will be described in detail with reference to the preferred embodiments.

In the formula (I), the chain hydrocarbon group for each of R^1, R^6 and R^9 may be alkyl, alkenyl or alkynyl. The monocyclic hydrocarbon group may be cycloalkyl, cycloalkenyl or phenyl. The polycyclic hydrocarbon group may be a condensed polycyclic hydrocarbon group such as naphthyl, tetrahydronaphthyl or indanyl, or a bridged polycyclic hydrocarbon group such as adamantyl, noradamantyl, norbornanyl or norbornanonyl. The monocyclic heterocycle group may be pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolinyl, pyrrolidinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, pyrazolinyl, hydantoinyl, oxazolinyl, isoxazolinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, dioxolanyl, dithiolanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, dihydropyridyl, tetrahydropyridyl, piperidinyl, dihydrooxopyridazinyl, tetrahydrooxopyridazinyl, dihydrooxopyrimidinyl, tetrahydrooxopyrimidinyl, piperazinyl, dihydropyranyl, tetrahydropyranyl, dioxanyl, dihydrodithinyl, dithianyl or morphorinyl. The polycyclic heterocycle group may be a condensed polycyclic heterocycle group such as thienothienyl, dihydrocyclopentathienyl, indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzimidazolyl, tetrahydrobenzothienyl, dihydrobenzofuranyl, tetrahydrobenzisoxazolyl, benzodioxolyl, quinolinyl, isoquinolinyl, benzodioxanyl or quinoxalinyl, or a bridged polycyclic heterocycle group such as quinuclidinyl.

The substituent for each of the chain hydrocarbon group which may be substituted for each of R^1, R^6 and R^9, the alkyl which may be substituted and the alkoxy which may be substituted for each of R^2 and R^7,

the alkyl which may be substituted, the alkenyl which may be substituted and the alkynyl which may be substituted for each of R^3, R^8 and R^{10}, the alkyl which may be substituted for each of R^4, R^5, R^{11} and R^{12} and the alkyl which may be substituted for X^3, may be a halogen atom, alkoxy, haloalkoxy, alkylthio, cycloalkyl, cycloalkoxy, cycloalkenyl, cycloalkenyloxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, aryl, aryloxy, arylthio, amino or alkyl-substituted amino. The number of such substituents or substituents on such substituents may be one or more. When the number is two or more, such substituents may be the same or different.

The substituent for each of the monocyclic hydrocarbon group which may be substituted, the polycyclic hydrocarbon group which may be substituted, the monocyclic heterocycle group which may be substituted and the polycyclic heterocycle group which may be substituted for each of R^1, R^6 and R^9, the phenyl which may be substituted and the phenoxy which may be substituted for each of R^2 and R^7, the cycloalkyl which may be substituted, the phenyl which may be substituted and the benzyl which may be substituted for each of R^3, R^8 and R^{10}, and the phenyl which may be substituted for X^3, may be a halogen atom, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, cycloalkyl, cycloalkoxy, cycloalkenyl, cycloalkenyloxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, aryl, aryloxy, arylthio, amino, alkyl-substituted amino, cyano or nitro. The number of such substituents or substituents for such substituents may be one or more. If the number is two or more, such substituents may be the same or different.

In the formula (I), the alkyl group and the alkyl moiety contained in each of X and Y may be C_{1-18} alkyl such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, decyl or nonadecyl, and they include linear or branched aliphatic structural isomers. The alkenyl group and the alkenyl moiety contained in each of X and Y may be C_{2-18} alkenyl such as vinyl, propenyl, butenyl, pentenyl, hexenyl, decenyl or nonadecenyl, and they include linear or branched aliphatic structural isomers. The alkynyl group and the alkynyl moiety contained in each of X and Y may be C_{2-18} alkynyl such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, decynyl or nonadecynyl, and they include linear or branched aliphatic structural isomers. The cycloalkyl group and the cycloalkyl moiety contained in each of X and Y may be c_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclooctyl. The cycloalkenyl group and the cycloalkenyl moiety contained in each of X and Y may be C_{5-8} cycloalkenyl such as cyclopentenyl, cyclohexenyl or cyclooctenyl. The halogen atom contained in each of X and Y may be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. The aryl group and the aryl moiety contained in each of X and Y may be phenyl, thienyl, furanyl, pyridyl, naphthyl, benzothienyl, benzofuranyl or quinolinyl.

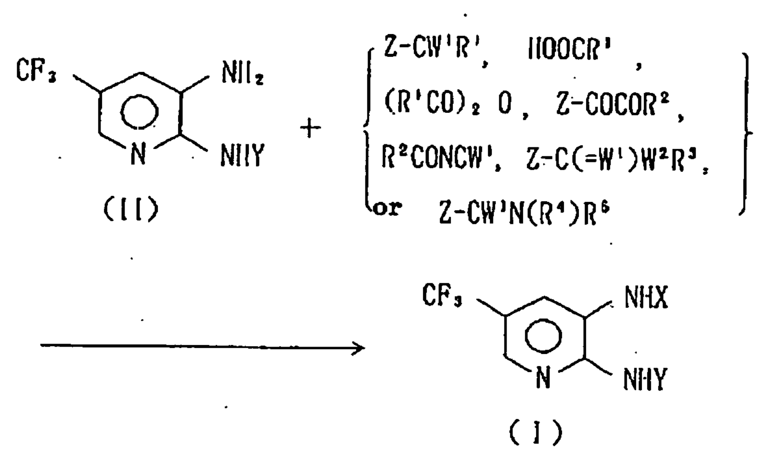
Now, preferred embodiments of the compound of the present invention will be described. In the formula (I), it is preferred that X is $-CW^1R^1$ or $-C(=W^1)W^2R^3$, and Y is $-SO_2R^9$. Each of R^1 and R^6 is preferably alkyl which may be substituted, alkenyl which may be substituted, cycloalkyl which may be substituted, cycloalkenyl which may be substituted, phenyl which may be substituted, tetrahydronaphthyl which may be substituted, indanyl which may be substituted or thienyl which may be substituted, more preferably, alkyl, haloalkyl, alkenyl, haloalkenyl, cycloalkyl, halogen-substituted cycloalkyl, phenyl, halogen-substituted phenyl, alkyl- or haloalkyl-substituted phenyl, or alkoxy- or haloalkoxy-substituted phenyl. Each of R^2 and R^7 is preferably alkoxy which may be substituted or phenyl which may be substituted, more preferably alkoxy, haloalkoxy, phenyl, or halogen-substituted phenyl. Each of R^3, R^8 and R^{10} is preferably alkyl which may be substituted, more preferably, alkyl or haloalkyl. Each of R^4, R^5, R^{11} and R^{12} is preferably alkyl. R^9 is preferably alkyl which may be substituted, alkenyl which may be substituted, cycloalkyl which may be substituted, cycloalkenyl which may be substituted or phenyl which may be substituted, more preferably alkyl, haloalkyl, phenyl, halogen-substituted phenyl, alkyl- or haloalkyl-substituted phenyl, or alkoxy- or haloalkoxy-substituted phenyl.

Preferred specific compounds of the present invention include N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)cyclohexanecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-5-indanecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)acetoxyacetamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)crotonamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-2-thiophenecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-trifluoromethylbenzamide, N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-fluorobenzamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-6-(1,2,3,4-tetrahydronaphthalene)carboxamide, N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)crotonamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-(2-thienyl)acrylamide, and their salts.

The compound of the formula (I) may form a salt when Y is $-SO_2R^9$ wherein R^9 is as defined above. Such a salt may be any pharmaceutically acceptable salt, for example, an alkali metal salt such as a potassium salt or a sodium salt, an alkaline earth metal salt such as a calcium salt, or an organic amine salt such as a triethanol amine salt or a tris(hydroxymethyl)aminomethane salt. Such a salt may have crystal water.

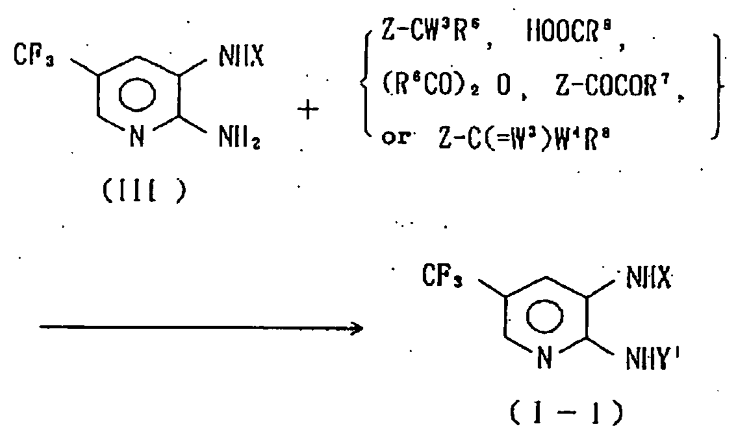
The compounds of the formula (I) and (I-1) can be prepared, for example, by processes represented by the following reactions (A) and (B):

Reaction (A)



In the above formulas, R^1, R^2, R^3, R^4, R^5, W^1, W^2, X and Y are as defined above, and Z is a halogen atom.

Reaction (B)



In the above formulas, Y^1 is $-CW^3R^6$, $-COCOR^7$ or $-C(=W^3)W^4R^8$, wherein R^6, R^7, R^8, W^3, W^4, X and Z are as defined above.

A compound of the formula (I-1) wherein X and Y^1 are the same substituents, can be prepared in the same manner as the Reaction (B) using as the starting material 2,3-diamino-5-trifluoromethylpyridine instead of the compound of the formula (III).

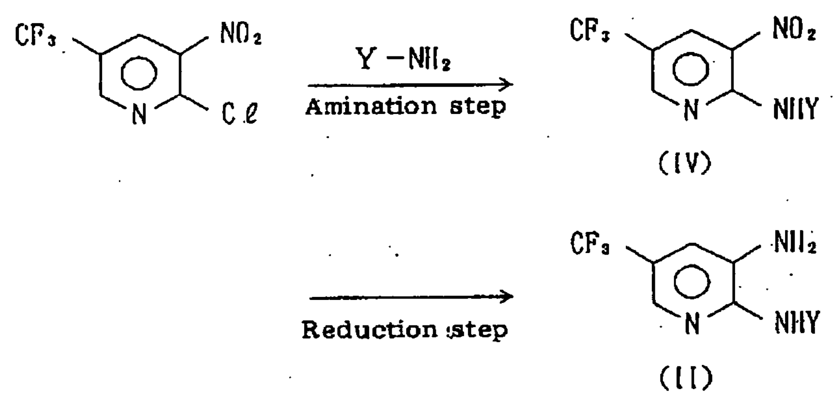
The reactions (A) and (B) are usually conducted in the presence of a solvent, if necessary, by using a base. The solvent may be an aromatic hydrocarbon such as benzene, toluene, xylene or chlorobenzene; a cyclic or non-cyclic aliphatic hydrocarbon such as chloroform, carbon tetrachloride, methylene chloride, dichloroethane, trichloroethane, n-hexane or cyclohexane; an ether such as diethyl ether, dioxane or

tetrahydrofuran; a ketone such as acetone, methyl ethyl ketone or methyl isobutyl ketone; a nitrile such as acetonitrile or propionitrile; an aprotic polar solvent such as dimethylformamide, N-methylpyrrolidone, dimethylsulfoxide or sulfolane. The base may be an inorganic base or an organic base. The inorganic base may, for example, be an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide; an alkali metal or alkaline earth metal carbonate such as anhydrous potassium carbonate or anhydrous calcium carbonate; an alkali metal hydride such as sodium hydride; or an alkali metal such as sodium metal. The organic base may be pyridine or triethylamine.

In the Reactions (A) and (B), a dehydrating condensation agent is required for the reaction with $HOOCR^1$ or $HOOCR^6$. Such a dehydrating condensation agent may be dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The reaction temperature is usually within a range of -30 to +100°C, preferably from 0 to 60°C, and the reaction time is usually within a range of from 1 to 24 hours, preferably from 1 to 10 hours.

The compound of the formula (II) can be prepared, for example, by processes represented by the following Reactions (C), (D) and (E):

Reaction (C)



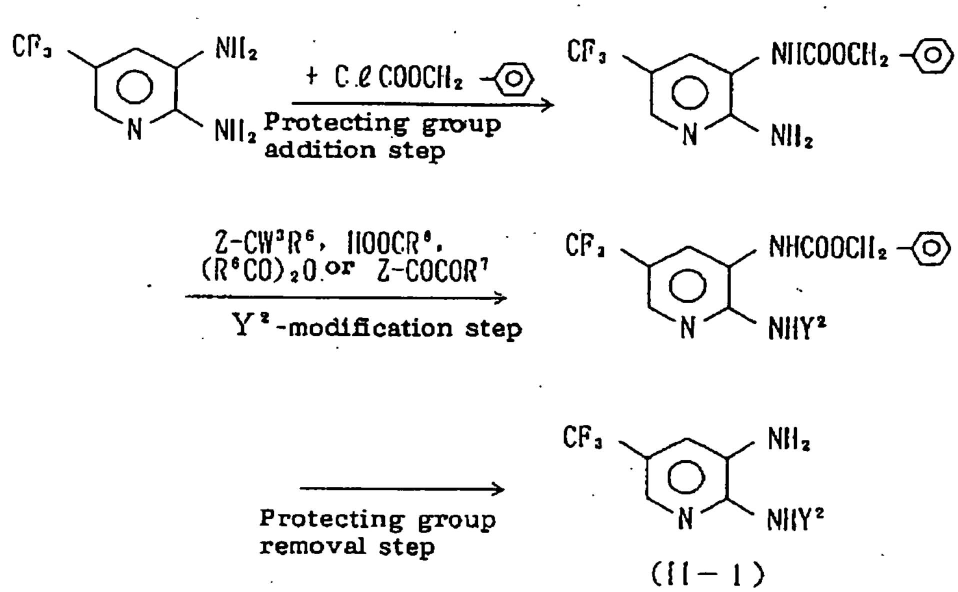
In the above formulas, Y is as defined above.

The amination step in the above Reaction (C) is conducted usually in the presence of a solvent, if necessary, by using a base. The solvent may be an aromatic hydrocarbon such as benzene, toluene, xylene or chlorobenzene; a cyclic or non-cyclic aliphatic hydrocarbon such as chloroform, carbon tetrachloride, methylene chloride, dichloroethane, trichloroethane, n-hexane or cyclohexane; an ether such as diethyl ether, dioxane or tetrahydrofuran; a nitrile such as acetonitrile or propionitrile; or an aprotic polar solvent such as dimethylformamide, N-methylpyrrolidone, dimethylsulfoxide or sulfolane. The base may be the same as the one useful for the above-mentioned Reactions (A) and (B). The reaction temperature is usually within a range of from -30 to +100°C, and the reaction time is usually from 1 to 24 hours.

The reduction reaction in the reduction step in the above Reaction (C) may be conducted by a method wherein an acid such as hydrochloric acid or acetic acid is used together with iron or zinc, a method wherein sodium hydrosulfide, potassium hydrosulfide, sodium sulfide, potassium sulfide or sodium hydrosulfite is used, or a method of catalytic hydrogenation wherein hydrogen is used in the presence of a palladium catalyst or a nickel catalyst. The solvent to be used for the reduction may be optionally selected depending upon the reduction method. Usually, an alcohol such as methanol, ethanol or propanol, water, acetic acid, ethyl acetate, dioxane, tetrahydrofuran or acetonitrile may be employed. The reaction temperature is usually from 0 to 100°C, and the reaction time is usually from 1 to 24 hours.

(i) In a case where Y is $-CW^3R^5$ or $-COCOR^7$

Reaction (D)

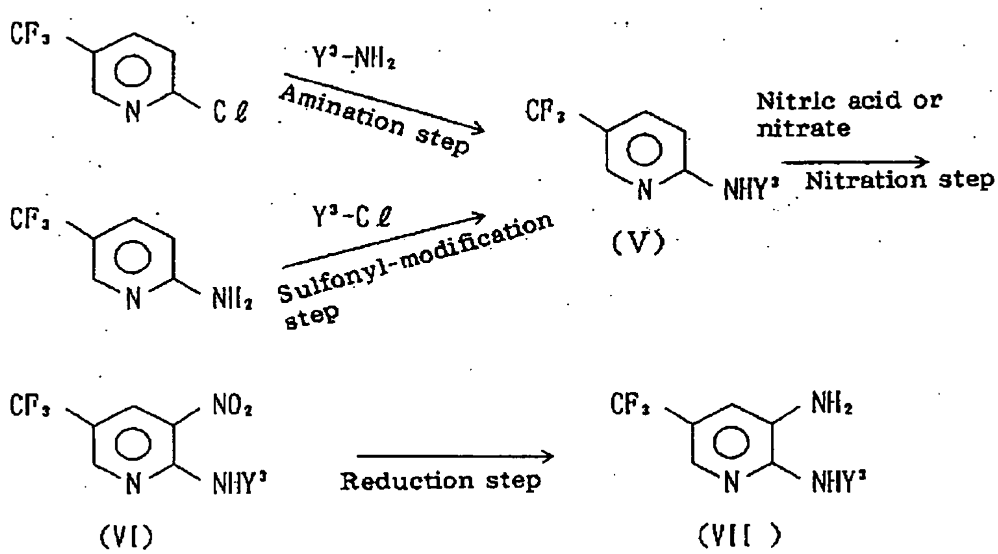


In the above formulas, Y^2 is $-CW^3R^6$ or $-COCOR^7$, wherein R^6, R^7, W^3 and Z are as defined above.

The protecting group addition step and the Y^2-modification step in the above Reaction (D) can be conducted in the same manner as in the above Reactions (A) and (B). Further, the protecting group removal step in the above Reaction (D) can be conducted by catalytic hydrogenation by means of a palladium catalyst such as palladium carbon usually in the presence of a solvent or by the hydrolysis usually in the presence of a solvent and an acid or base. The solvent may be water; an alcohol such as methanol or ethanol; or an ether such as diethyl ether, dioxane or tetrahydrofuran. The acid may be hydrobromic acid or trifluoroacetic acid. The base may be lithium hydroxide, potassium hydroxide, sodium hydroxide, potassium carbonate or sodium carbonate. The reaction temperature is usually from 0 to 100 °C, and the reaction time is usually from 1 to 24 hours.

(ii) In a case where Y is $-SO_2R^9$'

Reaction (E)



In the above formulas, Y^3 is $-SO_2R^{9'}$, $R^{9'}$ is alkyl which may be substituted, alkenyl which may be substituted, cycloalkyl which may be substituted or cycloalkenyl which may be substituted.

The amination step in the above Reaction (E) can be conducted usually in the presence of a solvent by means of a base. The solvent may be an aprotic polar solvent such as dimethyl acetamide, 1,3-dimethyl-2-imidazolidinone or dimethylsulfoxide. The base may be an inorganic base, for example, an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate such as anhydrous potassium carbonate or anhydrous sodium carbonate. The reaction temperature is usually from 80 to 150°C, and the reaction time is usually from 1 to 10 hours.

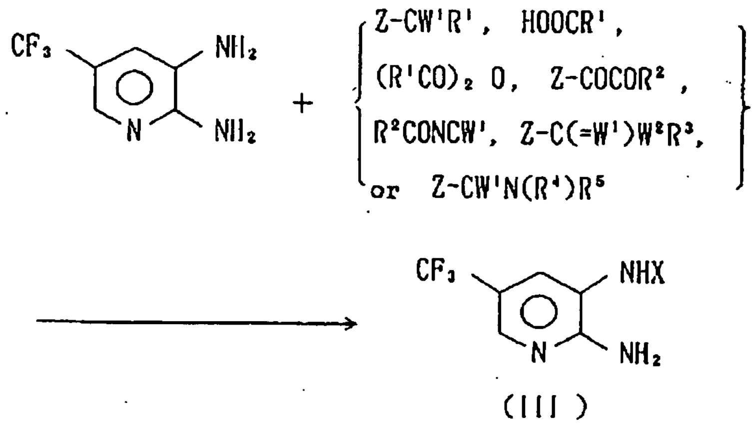
The sulfonyl-modification step in the above Reaction (E) can be conducted in the same manner as in the above Reactions (A) and (B).

The nitration step in the above Reaction (E) can be conducted by reacting with nitric acid or nitrate usually in the presence of a solvent. The nitrate may be sodium nitrate or potassium nitrate. The solvent may be acetic acid, acetic anhydride or trifluoroacetic acid. The reaction temperature is usually from 50 to 120°C, and the reaction time is usually from 1 to 10 hours.

The reduction step in the above Reaction (E) can be conducted in the same manner as the reduction step in the above Reaction (C).

The compound of the above formula (III) can be prepared, for example, by a process represented by the following Reaction (F).

Reaction (F)

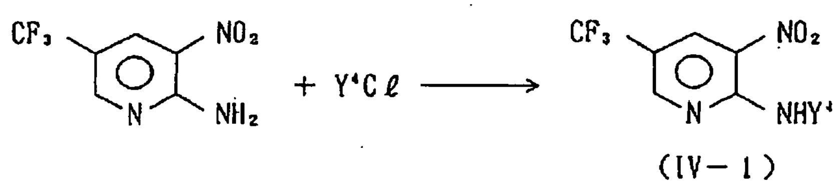


In the above formulas, R^1, R^2, R^3, R^4, R^5, W^1, W^2, X and Z are as defined above.

The above Reaction (F) can be conducted in the same manner as the above Reactions (A) and (B).

Among the compounds of the formula (IV), those wherein Y is $-SO_2R^9$, $-SO_2OR^{10}$ or $-SO_2N(R^{11})R^{12}$, can be produced also by a process represented by the following Reaction (G).

Reaction (G)

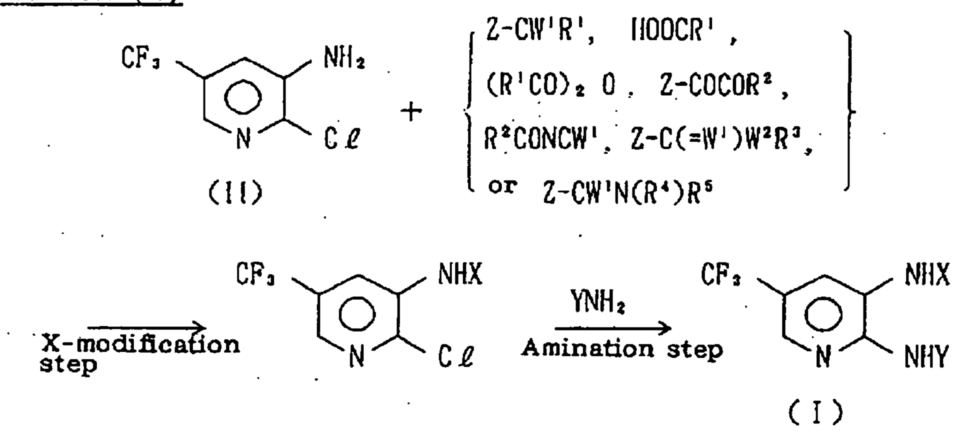


In the above formulas, Y^4 is $-SO_2R^9$, $-SO_2OR^{10}$ or $-SO_2N(R^{11})R^{12}$, wherein R^9, R^{10}, R^{11} and R^{12} are as defined above.

The above Reaction (G) can be conducted in the same manner as the sulfonyl-modification step in the above Reaction (E).

The compound of the formula (I) can also be prepared by the following alternative method represented by a Reaction (H).

Reaction (H)

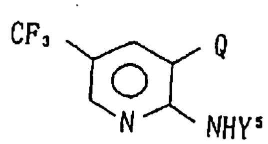


In the above formulas, R^1, R^2, R^3, R^4, R^5, W^1, W^2, X, Y and Z are as defined above.

The X-modification step in the above Reaction (H) can be conducted in the same manner as the above Reaction (A), and the amination step is conducted in the same manner as the amination step in the above Reaction (C).

Among the compounds of the above formulas (II), (IV), (IV-1), (V), (VI) and (VII), the following compounds are novel compounds and can be produced by the above Reactions (C), (E) and (G).

Trifluoromethylpyridine derivatives of the formula (VIII):



(VIII)

wherein Q is a hydrogen atom, nitro or amino, and Y^5 is $-(NH)_m-SO_2R^9$ wherein R^9 and m are as defined above, $-(NH)_m-SO_2OR^{10}$ wherein R^{10} and m are as defined above, or $-(NH)_m-SO_2N(R^{11})R^{12}$ wherein R^{11}, R^{12} and m are as defined above, provided that when Q is a hydrogen atom and m is 0, R^9 is other than naphthyl or phenyl which may be substituted.

Now, Preparation Examples for the compounds of the present invention will be described.

PREPARATION EXAMPLE 1

Preparation of N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)pentafluoropropionamide (Compound No. 19)

(1) 3.1 g of ethanesulfonamide was dissolved in 50 ml of dry tetrahydrofuran, and 1.2 g of 60% sodium hydride was added thereto under cooling with ice. After completion of the addition, the mixture was reacted for one hour under reflux. After cooling, 5.0 g of 2-chloro-3-nitro-5-trifluoromethylpyridine was added thereto, and then the mixture was reacted for 7 hours under reflux. After completion of the reaction, the reaction product was poured into 200 ml of water. Undissolved materials in water were extracted with ethyl ether and removed. Then, the aqueous layer was weakly acidified with dilute hydrochloric acid. Precipitated crystals were collected by filtration and dried to obtain 3.6 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)ethanesulfonamide having a melting point of from 160 to 163 °C.

(2) 1.5 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)ethanesulfonamide obtained in the above step (1) was dissolved in 30 ml of methanol, and 0.2 g of 5% palladium/carbon was added thereto, and a reduction reaction was conducted under a hydrogen pressure overnight under stirring. After completion of the reaction, 5% palladium/carbon was separated by filtration, and the solvent was distilled off under reduced pressure. The obtained crystals were washed with n-hexane and dried to obtain 1.2 g of N-(3-amino-5-

trifluoromethyl-2-pyridyl)ethanesulfonamide having a melting point of from 118 to 120°C.

(3) 0.50 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)ethanesulfonamide obtained in the above step (2) was suspended in 10 ml of dry diethyl ether, and 1.15 g of perfluoropropionic anhydride was dropwise added under cooling with ice. After the dropwise addition, the mixture was stirred for one hour and further reacted at room temperature for one hour. After completion of the reaction, the reaction product was poured into ice water and extracted with ethyl acetate. The extract layer was washed with water and dried, and the solvent was distilled off under reduced pressure. The obtained crystals were washed with n-hexane/ethyl ether to obtain 0.58 g of the desired product (Compound No. 19) having a melting point of from 168 to 170°C.

PREPARATION EXAMPLE 2

Preparation of N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-4-fluorobenzamide (Compound No. 10)

(1) 4.4 g of methanesulfonamide was dissolved in 70 ml of dry tetrahydrofuran, and 1.9 g of 60% sodium hydride was added thereto under cooling with ice. After completion of the addition, the mixture was reacted for one hour under reflux. After cooling, 7.0 g of 2-chloro-3-nitro-5-trifluoromethylpyridine was added thereto, and the mixture was reacted for 6 hours under reflux. After completion of the reaction, the reaction product was poured into 300 ml of water and washed with ethyl ether. Then, the aqueous layer was weakly acidified with dilute hydrochloric acid. Precipitated crystals were collected by filtration and dried to obtain 5.8 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)methanesulfonamide having a melting point of from 138 to 139°C.

(2) 4.0 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)methanesulfonamide obtained in the above step (1) was dissolved in 66 ml of methanol, and 0.4 g of 5% palladium/carbon was added thereto. A reduction reaction was conducted under a hydrogen pressure overnight under stirring. After completion of the reaction, 5% palladium/carbon was separated by filtration, and the solvent was distilled off under reduced pressure. The obtained crystals were washed with n-hexane and dried to obtain 3.2 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)methanesulfonamide having a melting point of from 128 to 130°C.

(3) 0.50 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)methanesulfonamideobtained in the above step (2) was dissolved in 6 ml of dry tetrahydrofuran, and 0.37 g of p-fluorobenzoyl chloride was dropwise added under cooling with ice. After the dropwise addition, the mixture was stirred for one hour and further reacted at room temperature overnight. After completion of the reaction, the reaction product was poured into ice water and extracted with ethyl acetate. The extract layer was washed with water and dried. The solvent was distilled off under reduced pressure, and the residue thereby obtained was crystallized from n-hexane/ethyl ether to obtain 0.61 g of the desired product (Compound No. 10) having a melting point of from 211 to 213°C.

PREPARATION EXAMPLE 3

Preparation of N-(3-trichloroacetylamino-5-trifluoromethyl-2-pyridyl)trifluoroacetamide (Compound No. 30)

(1) Into 38 ml of dry tetrahydrofuran, 1.5 g of 2,3-diamino-5-trifluoromethylpyridine was dissolved, and a solution mixture comprising 1.54 g of trichloroacetyl chloride and 3.8 ml of dry tetrahydrofuran was dropwise added thereto over a period of 10 minutes. Then, the mixture was reacted at room temperature for 3 hours. After completion of the reaction, precipitated crystals were collected by filtration and washed with tetrahydrofuran to obtain 2.2 g of N-(2-amino-5-trifluoromethyl-3-pyridyl)trichloroacetamide having a melting point of from 210 to 223°C.

(2) 2.20 g of N-(2-amino-5-trifluoromethyl-3-pyridyl)trichloroacetamideobtained in the above step (1) was dissolved in 45 ml of dry tetrahydrofuran, and a solvent mixture comprising 2.15 g of trifluoroacetic anhydride and 3 ml of dry tetrahydrofuran was dropwise added thereto under cooing with ice. After the dropwise addition, the mixture was reacted at room temperature for 3 hours. After completion of the reaction, the solvent was distilled off under reduced pressure, and the obtained crystals were washed with ethyl ether to obtain 1.20 g of the desired product (Compound No 30) having a melting point of from 166 to 168°C.

PREPARATION EXAMPLE 4

Preparation of N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)cyclohexanecarboxamide (Compound No.

471

(1) 20.3 g of ethanesulfonamide and 28.0 g of 2-chloro-5-trifluoromethylpyridine were dissolved in 220 ml of dimethylsulfoxide, and 47.4 g of anhydrous potassium carbonate was further added thereto. This solution mixture was heated to 130°C and reacted for 5 hours. After completion of the reaction, the reaction product was poured into 1 ℓ of water. Undissolved materials in water were extracted with ethyl ether and removed. Then, the aqueous layer was adjusted to pH4 with concentrated hydrochloric acid, and precipitated crystals were collected by filtration and dried to obtain 28.2 g of N-(5-trifluoromethyl-2-pyridyl)ethanesulfonamide having a melting point of from 164 to 165°C.

(2) 45 g of N-(5-trifluoromethyl-2-pyridyl)ethanesulfonamide was dissolved in 112.5 ml of acetic acid. While heating it to a temperature of from 100 to 105°C, 28 g of fuming nitric acid (94%) was dropwise added, and the mixture was reacted for further 6 hours. The reaction product was left to cool to 80°C, and then poured into 2 ℓ of ice water. Precipitated crystals were collected by filtration, washed with water and dried to obtain 47.8 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)ethanesulfonamide.

(3) 3.0 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)ethanesulfonamide was suspended in a solvent mixture comprising 30 ml of water and 30 ml of acetic acid, and 2.2 g of reduced iron was added thereto. Then, the mixture was heated to 50°C and reacted for one hour. After completion of the reaction, the reaction product was cooled to room temperature, and excess iron was separated by filtration. The filtrate was extracted with ethyl acetate. The extract layer was washed with water and dried. Ethyl acetate was distilled off under reduced pressure to obtain 2.5 g of N-(3-amino-5-trifluoromethylethyl-2-pyridyl)-ethanesulfonamide.

An alternative process will be described. To a solution prepared by dissolving 34.9 g of sodium hydrosulfite in 400 ml of water, a solution prepared by dissolving 5.0 g of N-(3-nitro-5-trifluoromethyl-2-pyridyl)ethanesulfonamide in 80 ml of tetrahydrofuran, was dropwise added at room temperature. After completion of the dropwise addition, the mixture was reacted for further 3 hours. After completion of the reaction, sodium chloride was added until the tetrahydrofuran layer was separated. The separated tetrahydrofuran layer was dried, and tetrahydrofuran was distilled off under reduced pressure to obtain 4.2 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)ethanesulfonamide.

(4) 2.36 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)ethanesulfonamide was dissolved in 24 ml of dry tetrahydrofuran, and 1.54 g of cyclohexanecarbonyl chloride was dropwise added thereto under cooling with ice. After the dropwise addition, the mixture was stirred for one hour and further reacted at room temperature overnight. After completion of the reaction, the solvent was distilled off under reduced pressure, the obtained crystals were washed with ethyl ether to obtain 2.94 g of the desired product having a melting point of from 153 to 155°C.

An alternative process will be described. In 20 ml of methylene chloride, 0.5 g of 4-diemthylaminopyridine was dissolved, and 0.78 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added and dissolved. Then, 1 g of N-(3-amino-5-trifluoromethyl-2-pyridyl)ethanesulfonamide was added thereto, and 30 minutes later, 0.52 g of cyclohexanecarboxylic acid was added thereto, and stirring was conducted for 10 hours. After completion of the reaction, 40 ml of methylene chloride was added to the reaction product, and the reaction product was washed with 10% hydrochloric acid and then washed with an aqueous sodium chloride solution and then dried over anhydrous sodium sulfate. From the extract layer, solvent was distilled off and the obtained residue was purified by silica gel column chromatography to obtain 0.88 g of the desired product.

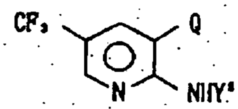
PREPARATION EXAMPLE 5

Preparation of sodium salt of N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)cyclohexanecarboxamide (Compound No. 251)

To 10 ml of an ethanol solution containing 1.00 g of N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)-cyclohexanecarboxamide, 2.75 g of a 1N-sodium hydroxide aqueous solution was added under stirring at 40°C, and the mixture was stirred for one hour. After completion of the reaction, the solvent was distilled off under reduced pressure, and the obtained crystals were washed with ethyl ether to obtain 1.02 g of the desired product which decomposed at 299°C.

Trifluoromethylpyridine compounds of the above formula (VIII) are listed in Table 1.

Table 1



(VIII)

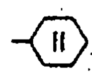
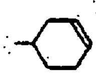
Intermediate No.	Q	Y^5	Melting point (°C)
1	H	$-SO_2CH_3$	189 ~ 191
2	H	$-SO_2C_2H_5$	164 ~ 165
3	H	$-SO_2CH_2CH_2CH_3$	157 ~ 159
4	H	$-SO_2CH_2CH_2CH_2CH_3$	148 ~ 150
5	H	$-SO_2CH<^{CH_3}_{CH_3}$	181 ~ 184
6	H	$-SO_2CH<^{CH_3}_{CH_2CH_3}$	
7	H	$-SO_2CH_2CH=CH_2$	
8	H	$-SO_2CH_2CH_2CH<^{CH_3}_{CH_3}$	
9	H	$-SO_2CH_2C(CH_3)=CH_2$	
10	H	$-SO_2CH_2CH_2OCH_2CH_3$	
11	H	$-SO_2CF_3$	215 ~ 218
12	H	$-SO_2$ 	
13	H	$-SO_2$ 	
14	H	$-SO_2$ 	
15	H	$-SO_2C_8H_{17}(n)$	

Table 1 (cont.)

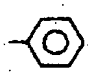
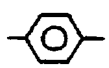
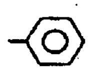
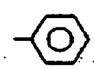
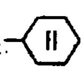
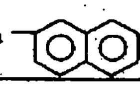
Intermediate No.	Q	Y'	Melting point (°C)
16	H	$-SO_2C_{18}H_{37}(n)$	
17	H	$-SO_2CF_2CF_3$	
18	NO_2	$-SO_2CH_3$	138 ~ 139
19	NO_2	$-SO_2CH_2CH_3$	160 ~ 163
20	NO_2	$-SO_2CH(CH_3)_2$	138 ~ 140
21	NO_2	$-SO_2CH_2CH_2CH_3$	109 ~ 112
22	NO_2	$-SO_2CH_2CH_2CH_2CH_3$	76 ~ 78
23	NO_2	$-SO_2-$ 	138 ~ 140
24	NO_2	$-SO_2-$  $-CH_3$	145 ~ 146
25	NO_2	$-NHSO_2CH_3$	175 ~ 182
26	NO_2	$-NHSO_2O-$ 	
27	NO_2	$-SO_2O-$ 	
28	NO_2	$-NHSO_2N(CH_3)_2$	
29	NO_2	$-SO_2CH_2C(CH_3)=CH_2$	51 ~ 56
30	NO_2	$-SO_2-$ 	156 ~ 158
31	NO_2	$-SO_2-$ 	

Table 1 (cont.)

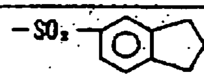
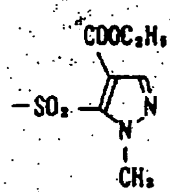
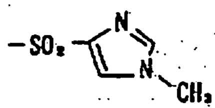
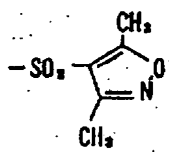
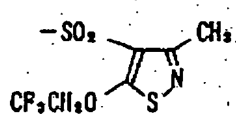
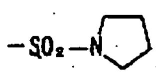
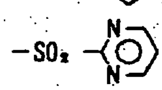
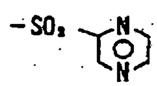
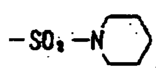
Intermediate No.	Q	Y'	Melting point (°C)
32	NO_2		
33	NO_2		
34	NO_2		130 ~ 132
35	NO_2		
36	NO_2		
37	NO_2		192 ~ 194
38	NO_2		
39	NO_2		
40	NO_2		
41	NO_2		

Table 1 (cont.)

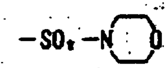
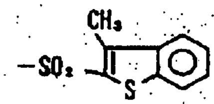
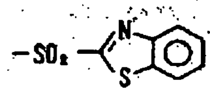
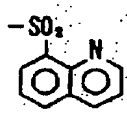
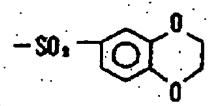
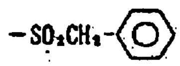
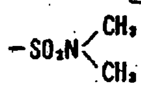
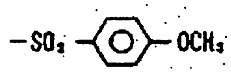
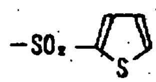
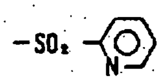
Intermediate No.	Q	Y*	Melting point (°C)
42	NO_2		
43	NO_2		
44	NO_2		
45	NO_2		
46	NO_2		
47	NO_2		
48	NO_2		148 ~ 149
49	NO_2		132
50	NO_2	$-SO_2CF_3$	126 ~ 127
51	NO_2	$-SO_2CH_3$	93 ~ 94
52	NO_2	$-SO_2C_2H_5$	120 ~ 121
53	NO_2		104 ~ 105
54	NO_2		

Table 1 (cont.)

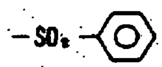
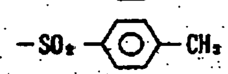
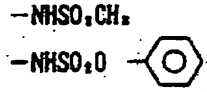
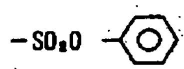
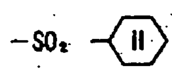
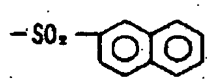
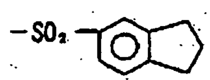
Intermediate No.	Q	Y^5	Melting point (°C)
55	NH_2	$-SO_2CH_3$	128 ~ 130
56	NH_2	$-SO_2CH_2CH_3$	118 ~ 120
57	NH_2	$-SO_2CH(CH_3)_2$	155 ~ 157
58	NH_2	$-SO_2CH_2CH_2CH_3$	82 ~ 84
59	NH_2	$-SO_2CH_2CH_2CH_2CH_3$	102 ~ 103
60	NH_2		200 ~ 204
61	NH_2		170 ~ 175
62	NH_2	$-NHSO_2CH_3$	128 ~ 133
63	NH_2		
64	NH_2		
65	NH_2	$-NHSO_2N(CH_3)_2$	
66	NH_2	$-SO_2CH_2C(CH_3)=CH_2$	136 ~ 139
67	NH_2		164 ~ 168
68	NH_2		
69	NH_2		

Table 1 (cont.)

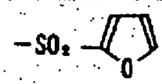
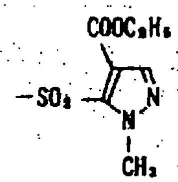
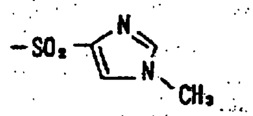
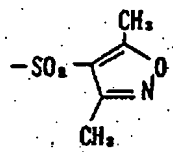
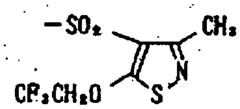
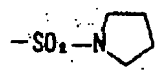
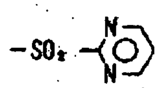
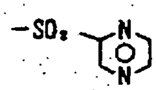
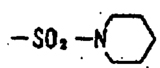
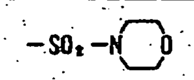
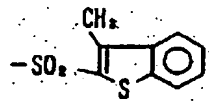
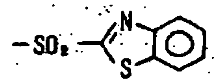
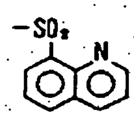
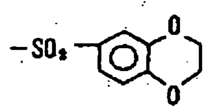
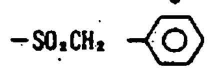
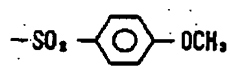
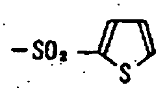
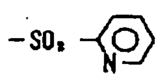
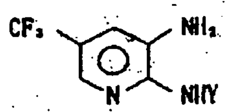
Intermediate No.	Q	Y^{s}	Melting point (°C)
70	NH_2		
71	NH_2		171 ~ 174
72	NH_2		
73	NH_2		
74	NH_2		168 ~ 173
75	NH_2		
76	NH_2		
77	NH_2		
78	NH_2		

Table 1 (cont.)

Intermediate No.	Q	Y'	Melting point (°C)
79	NH_2		
80	NH_2		
81	NH_2		
82	NH_2		
83	NH_2		
84	NH_2		
85	NH_2	$-SO_2N(CH_3)_2$	165 ~ 167
86	NH_2		134 ~ 136
87	NH_2	$-SO_2CF_3$	122 ~ 124
88	NH_2	$-SO_2CH_3$	97 ~ 100
89	NH_2	$-SO_2C_2H_5$	131 ~ 132
90	NH_2		223 ~ 227
91	NH_2		

Compounds of the above formula (II) which are not included in the compounds of the above formula (VIII) are listed in Table 2.

Table 2



(II)

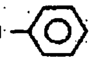
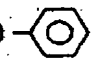
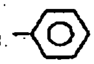
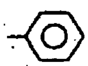
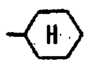
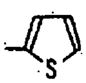
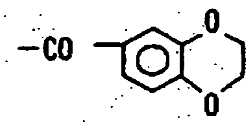
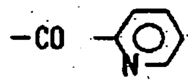
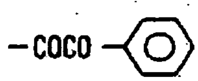
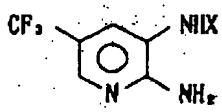
Intermediate No..	Y	Melting point (°C)
100	—NHCO— 	207 ~ 210
101	$-NHCOOCH_2CH_3$	187 ~ 192
102	$-COOCH_2CH_3$	289 ~ 292
103	$-NHCOCH_3$	
104	—COO— 	
105	$-COSCH_2-$ 	
106	$-CH_3$	
107	$-CH_2CH_3$	
108	$-COCH_3$	
109	$-COCH_2CH=CH_2$	
110	—CO— 	
111	—CO— 	
112	—CO— 	

Table 2 (cont.)

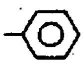
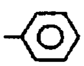
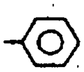
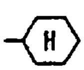
Intermediate No.	Y	Melting point (°C)
113		
114		
115		
116	$-COCOCH_3$	
117		

Compounds of the above formula (III) are listed in Table 3.

Table 3

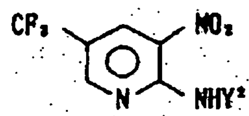


(III)

Intermediate No.	X	Melting point (°C)
118	$-COCHC\ell_2$	170 ~ 171
119	$-COCC\ell_3$	141 ~ 143
120	$-COOCH_2CH_3$	151 ~ 154
121	$-COOCH_2-$ 	156 ~ 158
122	$-COCOCH_3$	
123	$-COCO-$ 	
124	$-CONHCOCH_3$	
125	$-CO-$ 	
126	$-CO-$ 	248 ~ 251

Compounds of the above formula (IV) which are not included in the compounds of the above formula (VIII) are listed in Table 4.

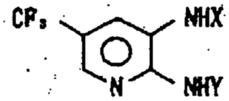
Table 4

 (IV)

Intermediate No.	Y^2	Melting point (°C)
127	$-NHCO-$	189 ~ 195
128	$-NHCOOCH_2CH_3$	97 ~ 99
129	$-NHCOCH_3$	
130	$-CH_3$	
131	$-CH_2CH_3$	

Typical specific examples of the compound of the formula (I) of the present invention are listed in Table 5.

Table 5



(I)

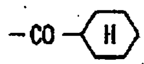
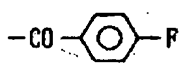
Compound No.	X	Y	Melting point (°C)
1	$-CO(CH_2)_2CH_3$	$-SO_2CH_3$	113 ~ 114
2	$-CO(CH_2)_3CH_3$	$-SO_2CH_3$	119 ~ 121
3	$-CO(CH_2)_4CH_3$	$-SO_2CH_3$	119 ~ 122
4	$-CO(CH_2)_7CH_3$	$-SO_2CH_3$	99 ~ 101
5	$-CO(CH_2)_{10}CH_3$	$-SO_2CH_3$	94 ~ 97
6	$-CO(CH_2)_{14}CH_3$	$-SO_2CH_3$	99 ~ 103
7	$-COCH_2C(CH_3)_3$	$-SO_2CH_3$	150 ~ 151
8		$-SO_2CH_3$	110 ~ 116
9	$-COCH=CH_2$	$-SO_2CH_3$	174 ~ 176
10		$-SO_2CH_3$	211 ~ 213
11	$-COCF_2C\ell$	$-SO_2CH_3$	199 ~ 201
12	$-COCF_3$	$-SO_2CH_3$	154 ~ 157
13	$-COCF_2CF_3$	$-SO_2CH_3$	186 ~ 189
14	$-COCF_2CF_2CF_3$	$-SO_2CH_3$	170 ~ 173
15	$-COOC_2H_5$	$-SO_2CH_3$	180 ~ 182
16	$-COO(CH_2)_2CH_3$	$-SO_2CH_3$	173 ~ 176
17	$-COO(CH_2)_3CH_3$	$-SO_2CH_3$	127 ~ 129

Table 5 (cont.)

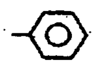
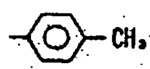
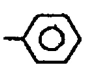
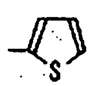
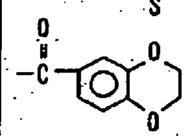
Compound No.	X	Y	Melting point (°C)
18	$-CSNHCOOC_2H_5$	$-SO_2CH_3$	More than 300
19	$-COCF_2CF_3$	$-SO_2C_2H_5$	168 ~ 170
20	$-COCF_2C\ell$	$-SO_2C_2H_5$	171 ~ 174
21	$-CSNHCOOC_2H_5$	$-SO_2C_2H_5$	More than 300
22	$-COCF_2CF_3$	$-SO_2C_3H_7(n)$	129 ~ 133
23	$-COCF_2CF_3$	$-SO_2C_8H_{17}(n)$	109 ~ 112
24	$-COCF_3$	$-SO_2-$ 	160 ~ 163
25	$-CSNHCOOC_2H_5$	$-SO_2-$ 	195 ~ 200
26	$-CO(CH_2)_2OC_2H_5$	$-CO(CH_2)_2OC_2H_5$	75 ~ 76
27	$-COCF_3$	$-COCHC\ell_2$	117 ~ 119
28	$-COCHC\ell_2$	$-COCHC\ell_2$	158 ~ 159
29	$-COCHC\ell_2$	$-COCF_3$	177 ~ 178
30	$-COCC\ell_3$	$-COCF_3$	166 ~ 168
31	$-COO-$ 	$-SO_2C_2H_5$	135 ~ 137
32	$-CO-$ 	$-COCF_2CF_3$	228 ~ 230
33	$-COCH_2-$ 	$-SO_2C_2H_5$	130 ~ 134
34		$-SO_2CH_3$	218 ~ 222

Table 5 (cont.)

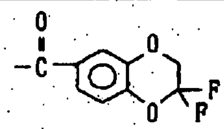
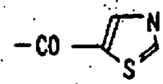
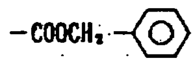
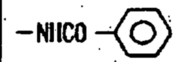
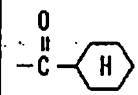
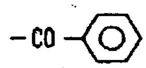
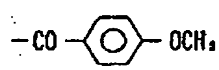
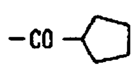
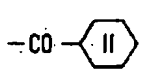
Compound No.	X	Y	Melting point (°C)
35		$-SO_2CH_3$	219 ~ 224
36		$-SO_2C_2H_5$	
37	$-COOC_2H_5$	$-COOC_2H_5$	112 ~ 114
38		$-COOC_2H_5$	134 ~ 137
39	$-COCF_2CF_3$		214 ~ 217
40	$-COCF_2CF_3$	$-NHSO_2CH_3$	136 ~ 138
41	$-COCF_2CF_3$	$-CH_3$	89 ~ 90
42		$-NHCCH_3$ (C=O)	
43		$-SO_2CH_3$	189 ~ 192
44		$-SO_2CH_3$	217 ~ 220
45		$-SO_2CH_3$	153 ~ 155
46	$-CO(CH_2)_4Cl$	$-SO_2CH_3$	79 ~ 85
47		$-SO_2CH_2CH_3$	153 ~ 155

Table 5 (cont.)

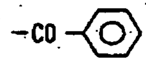
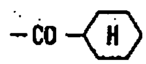
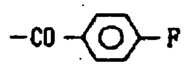
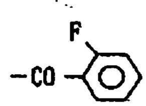
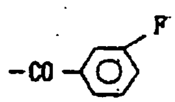
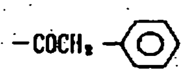
Compound No.	X	Y	Melting point (°C)
48		$-SO_2CH_2CH_3$	204 ~ 210
49	$-COCH=CH_2$	$-SO_2CH_2CH_3$	148 ~ 151
50	$-COCCl_3$	$-SO_2CH(CH_3)_2$	178 ~ 180
51	$-COCF_2CF_3$	$-SO_2CH(CH_3)_2$	161 ~ 163
52	$-COCF_2CF_3$	$-SO_2CH_2CH_2CH_2CH_3$	146 ~ 149
53		$-SO_2CH_2CH_2CH_2CH_3$	152 ~ 154
54	$-CSNHCOOC_2H_5$	$-CH_3$	191 ~ 193
55	$-COCH=CHCH_3$	$-SO_2CH_3$	158 ~ 161
56		$-SO_2C_2H_5$	234 ~ 237
57		$-SO_2CH_3$	210 ~ 214
58		$-SO_2CH_3$	220 ~ 222
59	$-CO-CF_2CF_2H$	$-SO_2C_2H_5$	
60		$-SO_2CH_3$	163 ~ 166

Table 5 (cont.)

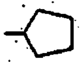
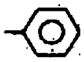
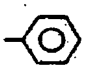
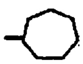
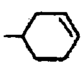
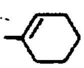
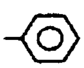
Compound No.	X	Y	Melting point (°C)
61	$-COCH_2-$ 	$-SO_2CH_3$	172 ～ 174
62	$-COCH_2-$ 	$-SO_2CH_3$	147 ～ 148
63	$-COCH_2OCOCH_3$	$-SO_2CH_3$	155 ～ 156
64	$-COCH_2CH_2-$ 	$-SO_2CH_3$	163 ～ 165
65	$-COCH(C_2H_5)(CH_2)_3CH_3$	$-SO_2CH_3$	141 ～ 144
66	$-COCH($  $)CH_2CH_3$	$-SO_2CH_3$	128 ～ 130
67	$-CO-$ 	$-SO_2CH_3$	126 ～ 130
68	$-CO-$ 	$-SO_2CH_3$	143 ～ 145
69	$-CO-$ 	$-SO_2CH_3$	176 ～ 179
70	$-COCH{=}C(CH_3)_2$	$-SO_2CH_3$	187 ～ 188
71	$-COCH{=}CH-$ 	$-SO_2CH_3$	215 ～ 218
72	$-COCH{=}CH-$ 	$-SO_2CH_3$	227 ～ 229
73	$-COCH{=}CHCH{=}CHCH_3$	$-SO_2CH_3$	300 以上
74	$-CO(CH_2)_2CH{=}CH_2$	$-SO_2CH_3$	91 ～ 93

Table 5 (cont.)

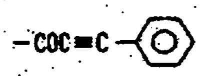
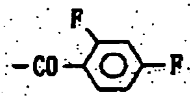
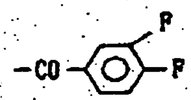
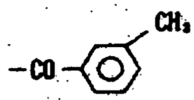
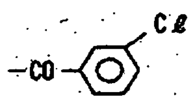
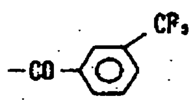
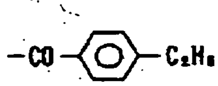
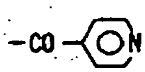
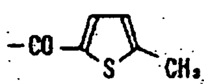
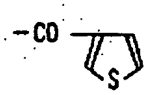
Compound No.	X	Y	Melting point (°C)
75		$-SO_2CH_3$	209 ~ 210
76		$-SO_2CH_3$	245 ~ 249
77		$-SO_2CH_3$	229 ~ 231
78		$-SO_2CH_3$	187 ~ 189
79		$-SO_2CH_3$	198 ~ 201
80		$-SO_2CH_3$	230 ~ 233
81		$-SO_2CH_3$	211 ~ 215
82		$-SO_2CH_3$	206 ~ 210
83		$-SO_2CH_3$	207 ~ 210
84		$-SO_2CH_3$	202 ~ 205

Table 5 (cont.)

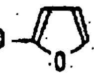
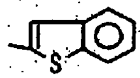
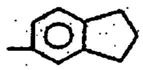
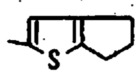
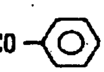
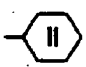
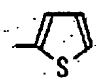
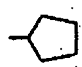
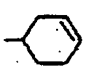
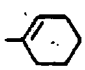
Compound No.	X	Y	Melting point (°C)
85	−CO 	$-SO_2CH_3$	227 ~ 231
86	−CO 	$-SO_2CH_3$	250 ~ 252
87	−CO 	$-SO_2CH_3$	194 ~ 197
88	−CO 	$-SO_2CH_3$	229 ~ 233
89	$-COCCl_2CH_3$	$-SO_2CH_3$	212 ~ 214
90	−COCO 	$-SO_2CH_3$	231 ~ 234
91	−CO 	$-SO_2CF_3$	175 ~ 178
92	−CO 	$-SO_2CF_3$	209 ~ 210
93	$-COCH=CHCH_3$	$-SO_2C_2H_5$	158 ~ 160
94	−CO 	$-SO_2C_2H_5$	157 ~ 161
95	−CO 	$-SO_2C_2H_5$	147 ~ 148
96	−CO 	$-SO_2C_2H_5$	163 ~ 165

Table 5 (cont.)

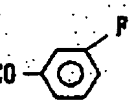
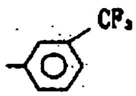
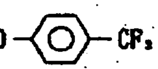
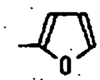
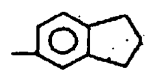
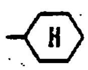
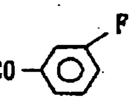
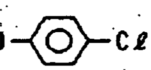
Compound No.	X	Y	Melting point (°C)
97	$-CO-$ 	$-SO_2C_2H_5$	163 ~ 166
98	$-CO-$ 	$-SO_2C_2H_5$	204 ~ 208
99	$-CO-$ 	$-SO_2C_2H_5$	215 ~ 218
100	$-CO-$ 	$-SO_2C_2H_5$	233 ~ 237
101	$-CO$ 	$-SO_2C_2H_5$	208 ~ 209
102	$-CO$ 	$-SO_2C_2H_5$	188 ~ 190
103	$-CO-$ 	$-SO_2C_3H_7$(iso)	152 ~ 154
104	$-CO-$ 	$-SO_2C_3H_7$(iso)	216 ~ 217
105	$-CO-$ 	$-SO_2C_3H_7$(iso)	227 ~ 230
106	$-COOC_3H_7$(n)	$-SO_2C_3H_7$(iso)	161 ~ 163
107	$-CO-$ 	$-SO_2C_4H_9$(n)	138 ~ 139

Table 5 (cont.)

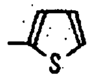
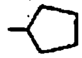
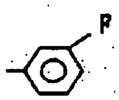
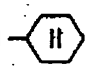
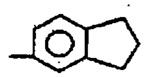
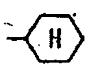
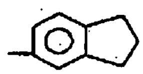
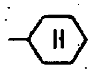
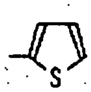
Compound No.	X	Y	Melting point (°C)
108	$-COCF_2Cl$	$-SO_2C_4H_9(n)$	156
109	$-CO$ 	$-SO_2$  OCH_3	202 ~ 205
110	$-CO(CH_2)_4CH_3$	$-SO_2N(CH_3)_2$	97
111	$-CO$ 	$-SO_2N(CH_3)_2$	168 ~ 169
112	$-COCF_2CF_3$	$-SO_2N(CH_3)_2$	157 ~ 159
113	$-CO$ 	$-SO_2N(CH_3)_2$	189 ~ 191
114	$-COOC_3H_7(n)$	$-SO_2N(CH_3)_2$	174 ~ 176
115	$-CO$ 	$-SO_2OCH_3$	147 ~ 148
116	$-CO$ 	$-SO_2OCH_3$	163 ~ 164
117	$-CO$ 	$-SO_2OC_2H_5$	140 ~ 141
118	$-CO$ 	$-SO_2OC_2H_5$	160 ~ 162
119	$-COCH_2$ 	$-SO_2C_2H_5$	137 ~ 139
120	$-CO$ 	$-SO_2CH_3$	202 ~ 203

Table 5 (cont.)

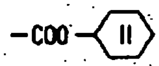
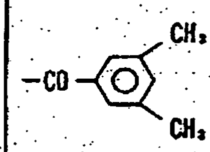
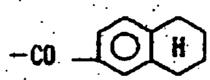
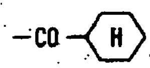
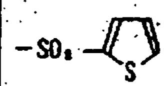
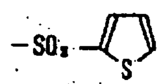
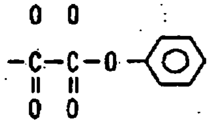
Compound No.	X	Y	Melting point (°C)
121		$-SO_2CH_3$	145 ~ 147
122		$-SO_2CH_3$	221 ~ 224
123		$-SO_2CH_3$	184 ~ 185
124	$-CO(CH_2)$[illegible]CH_3	$-SO_2CH_3$	94 ~ 96
125	$-CO(CH_2)$[illegible]CH_3	$-SO_2CH_3$	94 ~ 96
126			178 ~ 180
127			226 ~ 228
128	$-C(=O)-C(=O)-OC_2H_5$	$-SO_2CH_3$	
129		$-SO_2CH_3$	
130	$-C(=O)-OCH_2CH=CH_2$	$-SO_2CH_3$	
131	$-C(=O)-OCH_2C\equiv CH$	$-SO_2CH_3$	

Table 5 (cont.)

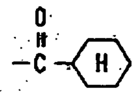
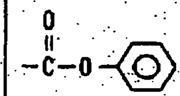
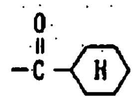
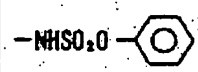
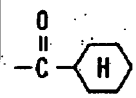
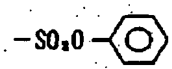
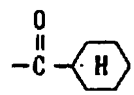
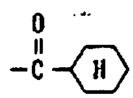
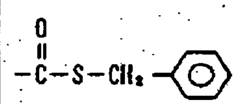
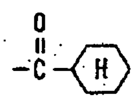
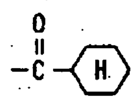
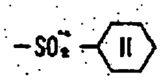
Compound No.	X	Y	Melting point (°C)
132	$-C(=O)-S-C_2H_5$	$-SO_2CH_3$	
133			
134			
135			
136	$-C(=O)N(CH_3)_2$	$-SO_2C_2H_5$	
137		$-NHSO_2N(CH_3)_2$	
138			
139		$-SO_2CH_2-C(CH_3)=CH_2$	138 ~ 140
140			190 ~ 192

Table 5 (cont.)

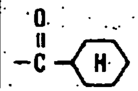
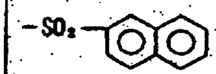
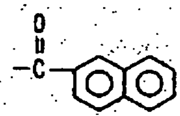
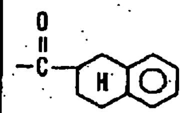
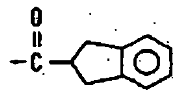
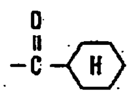
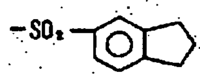
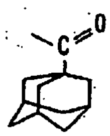
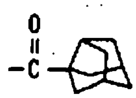
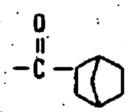
Compound No.	X	Y	Melting point (°C)
141			
142		$-SO_2C_2H_5$	210 ~ 211
143		$-SO_2C_2H_5$	
144		$-SO_2C_2H_5$	
145			
146		$-SO_2C_2H_5$	
147		$-SO_2C_2H_5$	
148		$-SO_2C_2H_5$	

Table 5 (cont.)

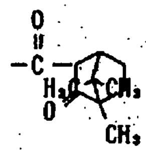
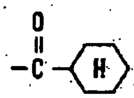
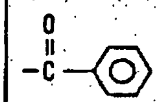
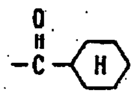
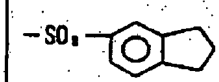
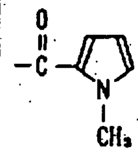
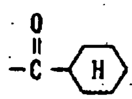
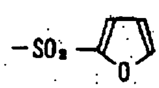
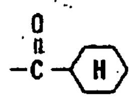
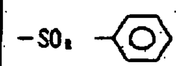
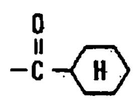
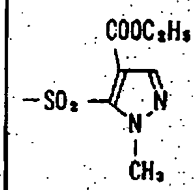
Compound No.	X	Y	Melting point (°C)
149		$-SO_2C_2H_5$	
150			
151			
152		$-SO_2C_2H_5$	
153			
154			166 ~ 167
155			144 ~ 146

Table 5 (cont.)

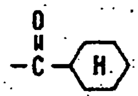
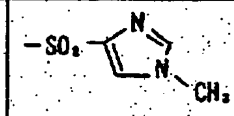
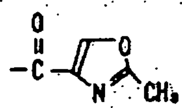
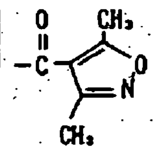
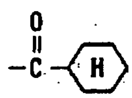
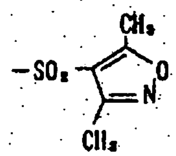
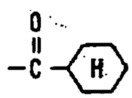
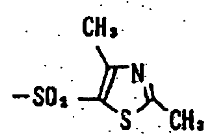
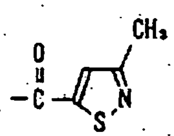
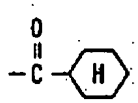
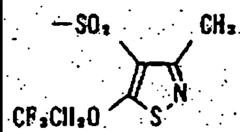
Compound No.	X	Y	Melting point (°C)
156			
157		$-SO_2C_2H_5$	
158		$-SO_2C_2H_5$	
159			
160			
161		$-SO_2C_2H_5$	
162			133 ~ 135

Table 5 (cont.)

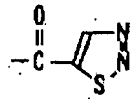
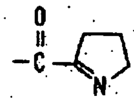
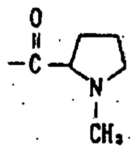
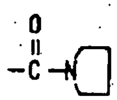
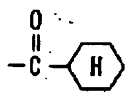
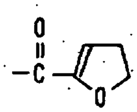
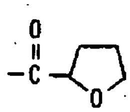
Compound No.	X	Y	Melting point (°C)
163		$-SO_2C_2H_5$	
164		$-SO_2C_2H_5$	
165		$-SO_2C_2H_5$	
166		$-SO_2C_2H_5$	
167		$-SO_2$ 	
168		$-SO_2C_2H_5$	
169		$-SO_2C_2H_5$	

Table 5 (cont.)

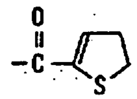
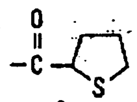
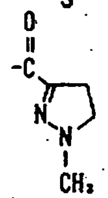
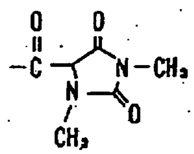
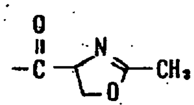
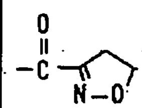
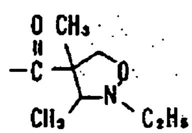
Compound No.	X	Y	Melting point (°C)
170		$-SO_2C_2H_5$	
171		$-SO_2C_2H_5$	
172		$-SO_2C_2H_5$	
173		$-SO_2C_2H_5$	
174		$-SO_2C_2H_5$	
175		$-SO_2C_2H_5$	
176		$-SO_2C_2H_5$	

Table 5 (cont.)

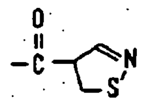
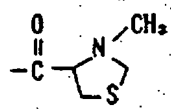
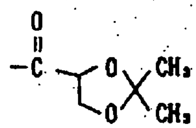
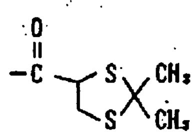
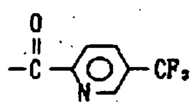
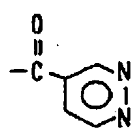
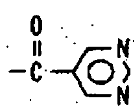
Compound No.	X	Y	Melting point (°C)
177		$-SO_2C_2H_5$	
178		$-SO_2C_2H_5$	
179		$-SO_2C_2H_5$	
180		$-SO_2C_2H_5$	
181		$-SO_2C_2H_5$	
182		$-SO_2C_2H_5$	
183		$-SO_2C_2H_5$	

Table 5 (cont.)

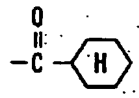
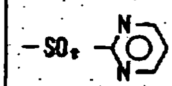
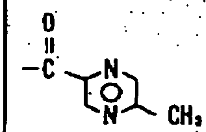
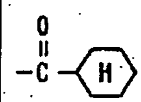
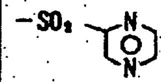
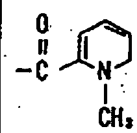
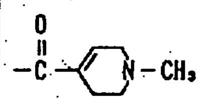
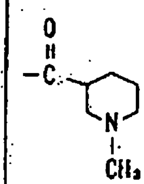
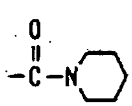
Compound No.	X	Y	Melting point (°C)
184			
185		$-SO_2C_2H_5$	
186			
187		$-SO_2C_2H_5$	
188		$-SO_2C_2H_5$	
189		$-SO_2C_2H_5$	
190		$-SO_2C_2H_5$	

Table 5 (cont.)

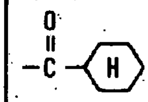
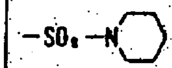
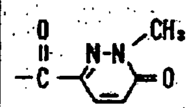
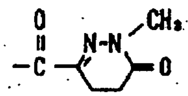
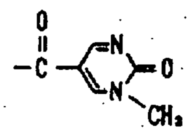
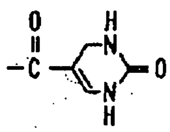
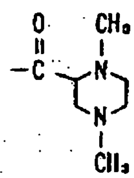
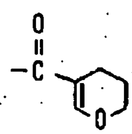
Compound No.	X	Y	Melting point (°C)
191			
192		$-SO_2C_2H_5$	
193		$-SO_2C_2H_5$	
194		$-SO_2C_2H_5$	
195		$-SO_2C_2H_5$	
196		$-SO_2C_2H_5$	
197		$-SO_2C_2H_5$	

Table 5 (cont.)

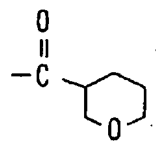
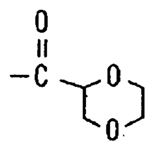
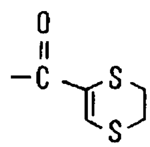
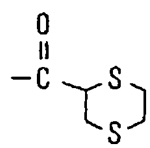
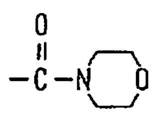
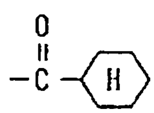
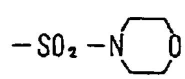
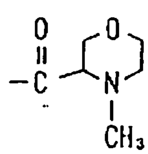
Compound No.	X	Y	Melting point (°C)
198		$-SO_2C_2H_5$	
199		$-SO_2C_2H_5$	
200		$-SO_2C_2H_5$	
201		$-SO_2C_2H_5$	
202		$-SO_2C_2H_5$	
203			
204		$-SO_2C_2H_5$	

Table 5 (cont.)

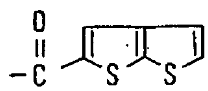
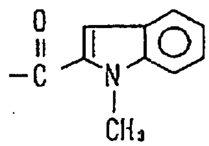
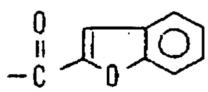
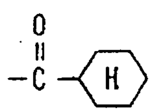
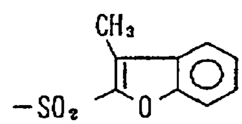
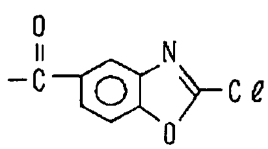
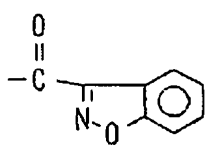
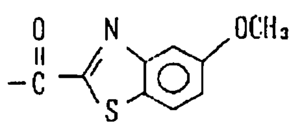
Compound No.	X	Y	Melting point (°C)
205		$-SO_2C_2H_5$	
206		$-SO_2C_2H_5$	
207		$-SO_2C_2H_5$	265 ~ 266
208			
209		$-SO_2C_2H_5$	
210		$-SO_2C_2H_5$	
211		$-SO_2C_2H_5$	

Table 5 (cont.)

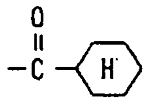
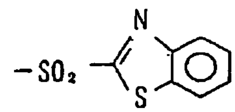
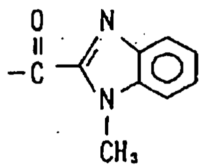
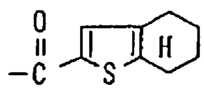
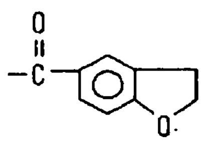
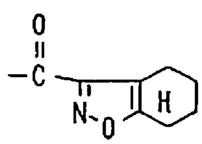
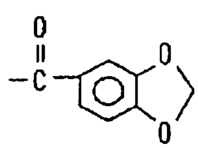
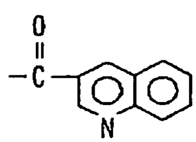
Compound No.	X	Y	Melting point (°C)
212			
213		$-SO_2C_2H_5$	
214		$-SO_2C_2H_5$	248 ～ 249
215		$-SO_2C_2H_5$	
216		$-SO_2C_2H_5$	
217		$-SO_2C_2H_5$	219 ～ 221
218		$-SO_2C_2H_5$	241 ～ 242

Table 5 (cont.)

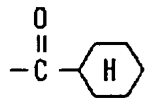
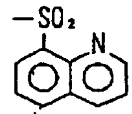
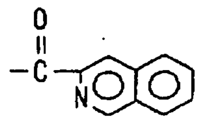
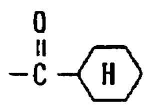
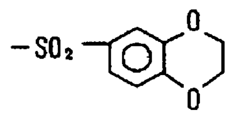
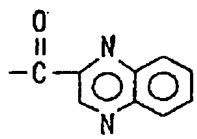
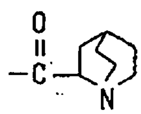
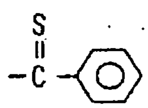
Compound No.	X	Y	Melting point (°C)
219			
220		$-SO_2C_2H_5$	
221			
222		$-SO_2C_2H_5$	
223		$-SO_2C_2H_5$	
224		$-SO_2C_2H_5$	
225	$-C(=O)-CH_2-OCH_2CF_3$	$-SO_2C_2H_5$	
226	$-C(=O)-CH_2SCH_3$	$-SO_2C_2H_5$	

Table 5 (cont.)

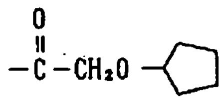
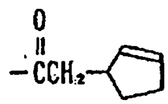
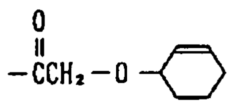
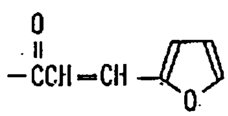
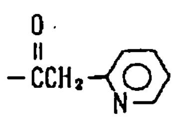
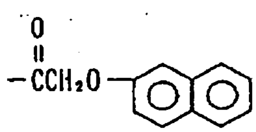
Compound No.	X	Y	Melting point (°C)
227		$-SO_2C_2H_5$	
228		$-SO_2C_2H_5$	
229		$-SO_2C_2H_5$	
230	$-\overset{O}{\overset{\|}{C}}CH_2COOCH_3$	$-SO_2C_2H_5$	
231	$-\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}CH_3$	$-SO_2C_2H_5$	
232		$-SO_2C_2H_5$	
233		$-SO_2C_2H_5$	
234		$-SO_2C_2H_5$	

Table 5 (cont.)

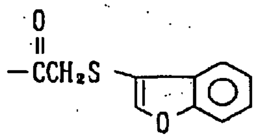
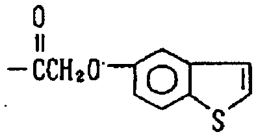
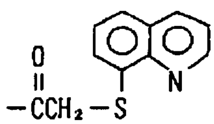
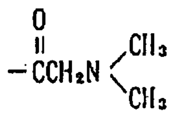
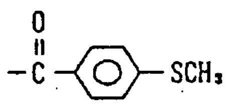
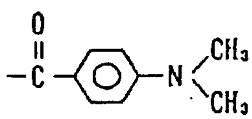
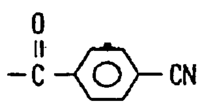
Compound No.	X	Y	Melting point (°C)
235		$-SO_2C_2H_5$	
236		$-SO_2C_2H_5$	
237		$-SO_2C_2H_5$	
238		$-SO_2C_2H_5$	
239		$-SO_2C_2H_5$	
240		$-SO_2C_2H_5$	
241		$-SO_2C_2H_5$	

Table 5 (cont.)

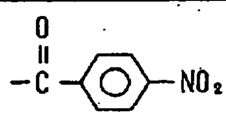
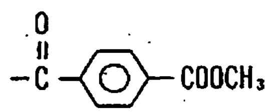
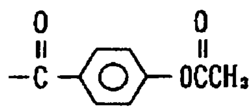
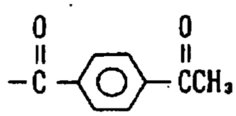
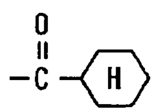
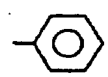
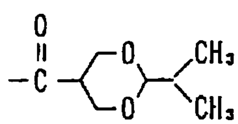
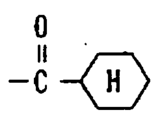
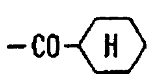
Compound No.	X	Y	Melting point (°C)
242		$-SO_2C_2H_5$	
243		$-SO_2C_2H_5$	
244		$-SO_2C_2H_5$	
245		$-SO_2C_2H_5$	
246		$-SO_2CH_2$ 	
247		$-SO_2C_2H_5$	
248		$-SO_2$ 	
249		$-SO_2C_3H_7(n)$	

Table 5 (cont.)

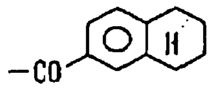
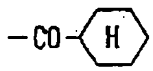
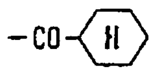
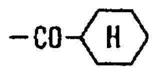
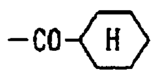
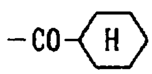
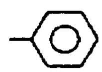
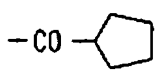
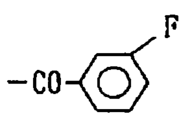
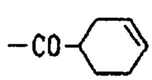
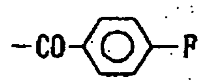
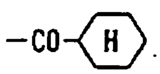
Compound No.	X	Y	Type of salt	Melting point (°C)
250		$-SO_2C_3H_7(n)$		
251		$SO_2C_2H_5$	Na salt	299 (decomposed)
252		$SO_2C_2H_5$	K salt	More than 300
253		$SO_2C_3H_7(iso)$	Na salt	
254		SO_2CF_3	Na salt	
255		SO_2 	Na salt	
256		$SO_2C_2H_5$	Na salt	
257		$SO_2C_2H_5$	Na salt	
258		$SO_2C_2H_5$	Na salt	

Table 5 (cont.)

Compound No.	X	Y	Type of salt	Melting point (°C)
259		$-SO_2CH_3$	Na salt	More than 300
260	$-COCF_2CF_3$	$-SO_2CH_3$	Na salt	More than 300
261	$-COCF_2CF_3$	$-SO_2C_2H_5$	Na salt	
262		$-SO_2C_2H_5$	Ca salt	245 (decomposed)

The compound of the formula (I) of the present invention is useful as an active ingredient for a phospholipase A_2 inhibitor, an anti-inflammatory agent or an anti-pancreatitis agent. Phospholipase A_2 can be detected in various tissues or cells in a body. It is said that in platelets or cells related to inflammatory symptoms, phospholipase A_2 is secreted or activated by various stimulations and contributes to the production of a platelet activating factor (PAF) or some arachidonic acid methabolites. The arachidonic acid methabolites have been found to be closely related to various diseases, for example, inflammatory symptoms such as rheumatoid arthritis, arthritis deformans, tenontitis, psoriasis and related dermatitis; nasal and bronchial airway troubles such as allergic rhinitis and allergic bronchial asthma; and immediate hypersensitive reactions such as allergic conjunctivitis. On the other hand, phospholipase A_2 secreted from pancreas is activated in the intestine and exhibits a digestive action, but once activated in the pancreas, it is believed to be one of the factors causing pancreatitis. The compound of the present invention inhibits phospholipase A_2 and thus is effective for the treatment of the above-mentioned diseases caused by phospholipase A_2 such as inflammatory symptoms, nasal and bronchial airway troubles, immediate hypersensitive reactions or pancreatitis. Thus, it is useful as an anti-inflammatory agent, an agent for treating bronchial asthma, an anti-allergy agent, an anti-pancreatitis agent, anti-nephritis agent, or anti-MOFC (Multiple Organ Failure).

In regard to the efficacy against pancreatitis, the compound of the present invention is expected to be more efficient by using in combination with other drugs, for example, a proteinase inhibitor, such as galexate mesilate, camostat mesilate, or nafamostat mesilate.

The compound of the present invention is particularly suitable for use as an anti-inflammatory agent and/or an anti-pancreatitis agent.

TEST EXAMPLE 1

Phospholipase A_2 inhibitory activity, method A

(1) Preparation of substrate

To 10 mg of egg yolk lecithin (manufactured by Wako Pure Chemical Industries Ltd.), 1 ml of glycerine, 2 ml of a 50 mM Tris-HCl buffer solution (pH7.5) [Tris(hydroxymethyl)aminomethane (manufactured by Nacalai Tesque K.K.) was adjusted to pH7.5 with hydrochloric acid], 0.5 ml of a 150 mM calcium chloride solution (calcium chloride was dissolved in a 50 mM Tris-HCl buffer solution) and 0.5 ml of a 0.05% Triton-X100 (manufactured by Nacalai Tesque K.K.) solution (Triton-X100 was dissolved in a 50 mM Tris-HCl buffer solution), were added and dispersed by an agate mortar or dispersed by an ultrasonic processor (Model W-225, manufactured by Heat System-Ultrasonics, Inc.) for 5 minutes (30W) to obtain a substrate.

(2) Enzyme

Porcine pancreatic phospholipase A_2 [(161454•122416) manufactured by Boehringer Mannheim•Yamanouchi K.K.] was used.

(3) Measurement of phospholipase A_2 activity

To a 96 well microtitration plate (flat bottom, manufactured by Sumitomo Bakelite Medical Co., Ltd.), 40 µl of the substrate, 5 µl of a solution prepared by dissolving 10 mg of a test compound in 500 µl of dimethylsulfoxide, followed by an addition of 500 µl of a 50 mM Tris-HCl buffer solution, and 5 µl of an enzyme solution of 20 ng/ml (prepared by diluting the enzyme in a 50 mM Tris-HCl buffer solution), were added and reacted at 37°C for 30 minutes. After termination of the reaction, the released free fatty acid was quantitatively analyzed in accordance with the ACS-ACOD (acyl CoA synthetase-acyl CoA oxidase) method [a kit of NEFA C test wako (manufactured by Wako Pure Chemical Industries, Ltd.) was used]. The quantitative analysis was made by means of Microplate ELISA Reader (Model 2550EIA Reader, manufactured by Bio-Rad Laboratories) at a wavelength of 540 nm. Separately, such experiments as mentioned above, were carried out at various concentrations (2 µg/ml, 1 µg/ml and 0.5 µg/ml) of phospholipase A_2 without a test compound. Then, the concentration of the free fatty acid versus the concentration of phospholipase A_2 was plotted.

From this standard curve, the apparent concentration of phospholipase A_2 in the case with a test compound, was read. Then, the percent inhibition of the enzyme was calculated by the following formula. The results are shown in Table 6.

Percent inhibition (%) = $(1 - \frac{A}{B}) \times 100$

A: Apparent enzyme concentration when a test compound is added.
B: True enzyme concentration when a test compound is added.

Table 6

Compound No.	% inhibition of PLA_2 (1,000 ppm)
1	45
2	55
3	67
4	74
5	39
8	81
9	71
10	60
11	52
12	89
13	87
14	54
15	62
16	43
17	46
18	64
19	>90
20	74
21	62
22	74
23	37
24	66
26	35

Table 6 (cont.)

Compound No.	% inhibition PLA2 (1,000 ppm)
27	62
28	71
29	47
30	87
32	50
38	35
39	41
41	89
43	47
44	43
45	50
46	47
47	75
48	48
49	30
50	78
51	63
52	49
53	37
54	37
55	49
57	57
58	74

TEST EXAMPLE 2

Phospholipase A_2 inhibitory activity, method B

(1) Preparation of substrate

To a solution prepared by dissolving 9.2 mg of L-α-dipalmitoylphosphatidylcholine (manufactured by Nichiyu Liposome K.K.) in 0.5 ml of chloroform, a solution prepared by dissolving 32 mg of sodium cholate (manufactured by Wako Pure Chemical Industries, Ltd.) in 0.5 ml of methanol, was added, followed by mixing. The solvent of the mixture was removed under a nitrogen stream, and then 2.5 ml of a 250 mM sodium chloride solution [prepared by dissolving sodium chloride in a 100 mM Tris-HCl buffer solution (tris-

(hydroxymethyl)aminomethane (manufactured by Nacalai Tesque K.K.) was adjusted to pH8.0 with hydrochloric acid}] was added thereto, and the mixture was dissolved under stirring to obtain a substrate.

(2) Enzyme

Porcine pancreatic phospholipase A_2 [(161454•122416) manufactured by Boehringer Mannheim•Yamanouchi K.K.] was used.

(3) Measurement of phospholipase A_2 activity

To a 96 well microtitration plate, 20 µl of a solution containing calcium chloride, bovine serum alubmin (manufactured by Sigma Chemical, Co.) and a Tris-HCl buffer solution (pH8.0) at concentrations of 25 mM, 4.5 mg/ml and 100 mM, respectively, 5 µl of a solution prepared by dissolving 10 mg of a test compound in 500 µl of diemthylsulfoxide, followed by an addition of 500 µl of a 200 mM Tris-HCl buffer solution, 5 µl of an enzyme solution (10 µg/ml) [prepared by dissolving the enzyme in a bovine serum alubmin solution (prepared by dissolving bovine serum alubmin in a 100 mM Tris-HCl buffer solution at a concentration of 1 mg/ml)] and 20 µl of the substrate, were added and reacted at 37°C for 30 minutes. After termination of the reaction, the released free fatty acid was quantitatively analyzed in accordance with the ACS-ACOD (acyl CoA synthetase-acyl CoA oxidase) method [a kit of NEFA C test wako (manufactured by Wako Pure Chemical Industries, Ltd.) was used]. The quantitative analysis was made by means of Microplate ELISA Reader (Model 2550EIA Reader, manufactured by Bio-Rad Laboratories) at a wavelength of 540 nm. Separately, such experiments as mentioned above, were carried out at various concentrations (1 µg/ml, 0.75 µg/ml, 0.5 µg/mol and 0.25 µg/ml) of phospholipase A_2 without a test compound. Then, the concentration of the free fatty acid versus the concentration of phospholipase A_2 was plotted.

From this standard curve, the apparent concentration of phospholipase A_2 in the case with a test compound, was read. Then, the percent inhibition of the enzyme was calculated by the following formula. The results are shown in Table 7.

$$\text{Percent Inhibition (\%)} = (1 - \frac{A}{B}) \times 100$$

A: Apparent enzyme concentration when a test compound is added.
B: True enzyme concentration when a test compound is added.

Table 7

Compound No.	% inhibition of PLA_2 (1,000 ppm)
7	50
10	51
13	51
18	49
19	75
43	49
44	64
45	41
47	90
53	100
58	42
60	41
61	36
62	53
63	34
64	61
65	71
66	52
67	82
68	81
69	63
70	40

Table 7 (cont.)

Compound No.	% inhibition of PLA_2 (1,000 ppm)
71	77
72	73
73	53
74	33
75	81
76	61
77	61
78	51
79	65
80	73
81	94
82	38
83	64
84	56
85	33
86	93
87	88
88	83
89	51
90	79
91	81
92	75
93	48
94	63
95	85
97	88
98	65
99	86
100	83

Table 7 (cont.)

Compound No.	% inhibition of PLA_2 (1,000 ppm)
103	86
104	61
106	78
108	61
109	67
110	58
111	41
112	79
113	35
114	53
115	52
116	69
117	65
118	84
121	90
122	56
123	86
124	78
125	86
126	84
127	89
251	85
259	61
260	53

TEST EXAMPLE 3

Inhibitory activity on increased vascular permeability induced by acetic acid (Mouse Whittle method, method C

Using ddy male mice, each test group consisted of 4 or 5 mice. A test compound was mixed with Tween 80 [polyoxyethylenesorbitan monooleate (manufactured by Nacalai Tesque K.K.)], and distilled water was added thereto to obtain a 2% Tween 80 suspension, or it was dissolved in the form of a salt in water to obtain an aqueous solution. A test compound was orally administered, and upon expiration of one hour from the administration, 0.7% acetic acid was intraperitonially injected to each mouse in an amount of 0.1 ml/10

g, and at the same time, 2% brilliant blue was intravenously injected into the tail vein in an amount of 0.1 ml/20 g. Thirty minutes after the injection of brilliant blue, the cervical vertebrae were dislocated under anesthesia by chloroform, and the abdominal cavity was washed with 5 ml of a physiological saline. The washing solution was subjected to centrifugal separation at 3,000 rpm for 10 minutes, and the amount of the dye in the supernatant was measured at 600 nm absorbance by Microplate ELISA Reader (Model 2550EIA Reader, manufactured by Bio-Rad Laboratories). The inhibition rate of the amount of leaked dye in the group in which a test compound was administered relative to the control group was obtained by the following formula. The results are shown in Table 8.

Inhibition rate (%) = $(1 - \frac{C}{D}) \times 100$

C: Amount of leaked dye in the group to which a test compound was administered.
D: Amount of leaked dye in the control group.

Table 8

Compound No.	Dose (mg/kg)	Inhibition rate (%)
1	50	46
2	20	51
3	50	58
4	50	43
5	50	53
7	20	53
8	20	48
9	50	81
10	25 10	53 42
11	100	49
13	100	57
15	50	41
16	20	55
17	50	31
18	25	49
20	20	48
22	20 10	81 39
23	20	33

Table 8 (cont.)

Compound	Dose (mg/kg)	Inhibition rate (%)
39	20	53
41	100	85
43	20	48
45	20	29
47	20 10	72 46
49	20	50
55	25	59
57	20	43
63	10	41
78	20 10	51 32
79	20	67
86	20	42
87	10	28
93	20 10	47 40
94	20	53
101	20	46
120	20	43
251	20	43

TEST EXAMPLE 4

Inhibitory activity on increased vascular permeability induced by acetic acid (Rat Whittle method, method D

Using SD (Crj: CD) male rats, each test group consisted of from 3 to 5 rats. A test compound was mixed with Tween 80 [polyoxyethylenesorbitan monooleate (manufactured by Nacalai Tesque K.K.)], and distilled water was added thereto to obtain a 2% Tween 80 suspension, or it was dissolved in the form of a salt in water to obtain an aqueous solution. A test compound was orally administered, and one hour later, 0.7% acetic acid was intraperitonially injected to each rat in an amount of 0.05 ml/10 g, and at the same time, 2% brilliant blue was intravenously injected into the tail vein in an amount of 0.05 ml/20 g. Thirty minutes after the injection of brilliant blue, the cervical vertebrae were dislocated under anesthesia by chloroform, and the abdorminal cavity was washed with 10 ml of a physiological saline. The washing solution was subjected to centrifugal separation at 3,000 rpm for 10 minutes, and the amount of the dye in the supernatant was measured at 600 nm absorbance by Microplate ELISA Reader (Model 2550EIA Reader, manufactured by Bio-Rad Laboratories). The inhibition rate of the amount of leaked dye in the group to which a test compound was administered relative to the control group was obtained from the following formula, and the results are shown in Table 9.

Inhibition rate (%) = $(1 - \frac{C}{D}) \times 100$

C: Amount of leaked dye in the group to which a test compound was administered.
D: Amount of leaked dye in the control group.

Table 9

Compound No.	Dose (mg/kg)	Inhibition rate (%)
2	100	38
3	100	75
10	100 50	57 37
16	100	96
17	50	40
19	50	34
20	100	49
22	100	58
23	100	40
43	50	72
45	50	27
46	50	31
47	50 25	82 56
49	50	30
55	25 12.5	69 43
57	50	47
58	50	31
60	50	72
61	25	61
63	50 25	39 31
66	25	72
69	25	48

Table 9 (cont.)

Compound No.	Dose (mg/kg)	Inhibition rate (%)
72	25	66
78	50 25	55 40
79	50	74
80	50 25	35 33
82	25	38
86	50	37
87	25 12.5	61 47
93	50 25	71 54
94	50 25	55 45
98	50	32
101	50	41
113	50	67
120	100 50	56 35
121	12.5	31
251	25 12.5	70 46

TEST EXAMPLE 5

Inhibitory activity on carrageenin edema

Using Wister male rats (body weight: about 100 g), each test group consisted of 5 rats. A test compound was mixed with Tween 80 [polyoxyethylenesorbitan monooleate (manufactured by Nacalai Tesque K.K.)], and distilled water was added thereto to obtain a 2% Tween 80 suspension, or it was dissolved in the form of a salt in water to obtain an aqueous solution. Either the suspension or the aqueous solution was orally administered in an amount of 200 mg/kg, 100 mg/kg, 50 mg/kg or 25 mg/kg. One hour later, 0.1 ml of a 1% λ-carrageenin solution dissolved in a physiological saline was injected subcutaneously to the right hind paw of each rat to cause inflamation. Three hours later, the paw volume was measured by a paw volume measuring device (manufactured by Ugobasiee K.K.). A swelling volume was obtained from the difference from the value before the inflammation. The inhibition rate was calculated by the following formula, and the results are shown in Table 10.

Inhibition rate (%) $= (1 - \frac{F}{E}) \times 100$

F: Average swelling volume in the group to which a test compound was administered.
E: Average swelling volume in the control group.

Table 10

Compound No.	Dose (mg/kg)	Inhibition rate (%)
2	100	17
3	100	20
5	100	37
10	100	28
11	100	24
13	100	21
16	100	24
19	100	31
22	100	29
23	100	30
25	200	27
28	50	25
39	100	25
43	50	31
45	50	23
46	50	30
47	50	41
57	100	35
60	50	27
65	50	37
66	50	31
67	25	19
69	50	25
72	25	21
73	50	20
77	50	22

Table 10 (cont.)

Compound No.	Dose (mg/kg)	Inhibition rate (%)
78	50	26
79	50	20
80	50	29
82	50	19
86	50	27
87	50	21
91	50	23
93	50	22
94	50	23
98	50	45
101	50	24
104	50	48
106	50	19
110	50	25
113	50	26
114	50	28
120	50	27
123	50	42
125	50	22
150	50	23
251	50	30
259	50	17

TEST EXAMPLE 6

Acute toxicity

Administration route: Intravenous injection

Using ddy male mice (body weight: 25 - 30 g), each test group consisted of 5 mice. A test compound was dissolved in the form of a sodium salt in a physiological saline or in a 5% glucose aqueous solution, and intravenously injected in an amount of 0.1 ml/10 g body weight. After the injection, the mortality rate was obtained over one week, and the median lethal dose LD_{50} (mg/kg) was determined. The results are shown in Table 11.

Table 11

Compound No.	LD_{50} (mg/kg)
1	100~150
2	50~100
3	>100
8	>25
9	>150
10	50~100
11	>150
12	>150
13	>70
15	100~150
16	>100
17	50~100
18	>150
19	50~100
21	>75
22	>100
24	>150
40	50~100
43	78

Table 11 (cont.)

Compound No.	LD_{50} (mg/kg)
45	98
47	58
49	175
55	237
57	83
60	>60
61	>80
63	>130
68	>80
73	>80
77	>80
78	>60
80	>80
86	>40
87	75
91	>80
106	>20
120	83
251	65

TEST EXAMPLE 7

Effects against acute pancreatitis

Using Crj-CD male rats (for Compound No. 19, rats having a body weight of from 371 to 484 g were used, and for Compound No. 10, rats having a body weight of from 444 to 574 g were used), each test group consisted of 3 rats. An experimental acute pancreatitis model was prepared by a closed duodenal loop method under anesthesia with halothane (manufactured by Hoechst Japan) and nitrous oxide (manufactured by Sumitomo Seika K.K.) applied by means of a general inhalation anesthesia machine (Model EM-2 and halothane evaporator F-Model). Then, Compound No. 19 or Compound No. 10 was

continuously intravenously injected into the tail vein in an amount of 50 mg per kg or 40 mg per kg, respectively, at a rate of 0.05 ml per minute by means of a pump (Technicon AA II Proportioning Pump III, manufactured by Technicon Instruments Corporation). No injection was made to a control group. Gross pathological examination was conducted upon expiration of 6 hours after the ventrotomy in the case of the test group to which Compound No. 19 was administered, or upon expiration of 3 hours after the ventrotomy in the case of the test group to which Compound No. 10 was administered. As a result, as shown in the following Table 12, the groups to which the compounds of the present invention were administered, show distinct usefulness for treating acute pancreatitis.

Table 12

Groups	Pancreatic hemorrhage Petechia		Pancreatic edema	
	Grade	Distribution	Grade	Distribution
Control group (against the group to which Compound No. 19 was administered)	++	++	++	++
	++	++	+++	++
	+++	+++	+++	++
Group to which Compound No. 19 was administered	—	—	+	+
	—	—	++	++
	—	—	+	+
Control group (against the group to which Compound No. 10 was administered)	++	++	++	++
	+	+	++	++
	±	±	++	++
Group to which Compound No. 10 was administered	±	±	±	±
	—	—	+	+
	+	+	++	+

Grade of pancreatic lesions
—: No significant lesions, ±: Minimal, +: Light, ++: Moderate, +++: Marked

Distribution of pancreatic lesions
—: No significant lesions, ± ~ +++: Focal-diffuse

TEST EXAMPLE 8

Effects against acute pancreatitis

Using Crj-CD male rats, each test group consisted of 3 rats. An experimental acute pancreatitis model was prepared by a closed duodenal loop method under anethesia with halothane (manufactured by Hoechst Japan) and nitrous oxide (manufactured by Sumitomo Seika K.K.) applied by a general inhalation anesthesia machine (Model EM2 and halothane evaporator F-Model). Each compound (subjected to the test in the form of a sodium salt) was continuously intravenously injected into the tail vein in an amount of 0.4 ml/100 g to 0.6 ml/100 g at a rate of 0.05 ml per minute by a pump (Technicon AA II Proportioning Pump III, manufactured by Technicon Instruments Corporation) or rapidly intravenously injected. No injection was made to a control group. Gross pathological examination was conducted upon expiration of 6 hours after the ventrotomy in the case of the group to which the compound was administered. With respect to each of four lesions among pancreatic lesions i.e. petechia, ecchymosis, pancreatic necrosis and abdominal fatty necrosis, the grade and the distribution of lesions were scored with five grades of 0, 0.5, 1, 2 and 3 (severe lesions are 3). The sum of all lesions was designated as scores of pancreatitis lesions, and the sum of the score of petechia and the score of ecchymosis only was designated as scores of hemorrhagic lesions. The pancreatitis inhibition rate (%) and the hemorrhage inhibition rate (%) were obtained by the following formulas, and the results are shown in Table 13.

$$\text{Pancreatitis inhibition rate (\%)} = \left(1 - \frac{H}{G}\right) \times 100$$

H: Scores of pancreatitis lesions of the group to which a test compound was administered.
G: Scores of pancreatitis lesions of the control group.

$$\text{Hemorrhage inhibition rate (\%)} = \left(1 - \frac{J}{I}\right) \times 100$$

J: Scores of hemorrhagic lesions of the group to which a test compound was administered.
I: Scores of hemorrhagic lesions of the control group.

Table 13

Compound No.	Dose (mg/kg)	*1	*2
1	10	66	49
2	26*	46	
3	10	49	51
9	10	36	21
11	23*	52	
13	23*	100	
14	19*	52	
15	10	45	61
16	20*	52	
17	20*	73	
21	27*	57	
24	11*	68	
34	10	30	30
35	10	35	35
43	20*	81	
45	25*	62	
46	46*	36	
47	20*	68	
49	42*	68	
55	40*	65	
57	20*	60	
58	10	70	51
60	10	92	94
61	10	79	64
62	10	45	61
63	10	83	66

Compound No.	Dose (mg/kg)	*1	*2
64	10	60	68
65	10	67	74
66	10	53	63
68	10	74	77
72	10	62	32
73	10	74	79
74	10	66	67
77	10	66	70
78	10	96	91
79	10	23	39
80	10	11	8
81	10	49	58
83	10	53	51
85	10	57	67
86	10	87	85
87	10	83	87
93	10	70	70
94	10	11	11
97	10	35	35
106	10	96	97
107	10	63	61
113	10	41	36
114	10	32	27
117	10	30	30
120	24*	100	
122	10	51	51
123	10	56	56
124	10	51	51
251	10	79	80

Note: Symbol * in the column for "Dose" indicates a case of continuous intravenous injection, and no symbol indicates a case of single intravenous injection.
*1: Inhibition rate of hemorrhagic lesions (%)
*2: Inhibition rate of pancreatitis lesions (%)

To administer the compound of the present invention for the treatment of the above-mentioned diseases caused by phospholipase A_2, it is formulated alone or together with a pharmaceutically acceptable carrier into a drug composition suitable for peroral, or parenteral administration, such as a tablet, a powder, a capsule, a granule, an injection drug, an ointment, an inhalant or a suppository, and it is administered in the form of such a drug formulation.

As a drug formulation suitable for peroral administration, a solid composition such as a tablet, a capsule, a powder, a granule or a troach; or a liquid composition such as a syrup suspension, may be mentioned. The solid composition such as a tablet, a capsule, a powder, a granule or a troach may contain a binder such as fine crystalline cellulose, gum arabic, tragacanth gum, gelatine or polyvinyl chloride; an excipient such as starch, lactose or carboxymethyl cellulose; a disintegrator such as arginic acid, corn starch or carboxymethyl cellulose; a lubricant such as magnesium stearate, light silicic anhydride or colloidal silicon dioxide; a sweetener such as sucrose; or a flavoring agent such as peppermint or methyl salicylate. The liquid composition such as a syrup or a suspension may contain sorbitol, gelatine, methyl cellulose, carboxymethyl cellulose, a vegetable oil such as a peanut oil, an emulsifier such as lecithin as well as a sweetener, a preservative, a colorant or a flavoring agent, as the case requires. Such a composition may be provided in the form of a dried formulation. These formulations preferably contain from 1 to 95% by weight of the active compound.

A drug formulation suitable for parenteral administration may, for example, be an injection drug. The injection drug may be prepared by dissolving the compound in the form of a salt in usual water for injection, or may be formulated into a formulation suitable for injection such as a suspension or an emulsion (in a mixture with a pharmaceutically acceptable oil or liquid). In such a case, it may contain benzyl alcohol as an antibacterial agent, ascorbic acid as an antioxidant, a pharmaceutically acceptable buffer solution or a reagent for adjusting the osmotic pressure. Such an injection drug preferably contains from 0.1 to 8% by weight of the active compound.

A drug formulation suitable for topical or per rectal administration may, for example, be an inhalant, an ointment or a suppository. The inhalant may be formulated by dissolving the compound of the present invention alone or together with a pharmaceutically acceptable inert carrier in an aerosol or nebulizer solution, or may be administered to the resiratory airway in the form of fine powder for inhalation. In the case of fine powder for inhalation, the particle size is usually not more than 50 μm, preferably not more than 10 μm. Such an inhalant may be used, if neccesary, in combination with other antiasthematic agent or bronchodilator.

An ointment may be prepared by a conventional method by an addition of a commonly employed base or the like. The ointment preferably contains from 0.1 to 30% by weight of the active compound.

The suppository may contain a carrier for formulation which is well known in this field, such as polyethylene glycol, lanolin, cacao butter or fatty acid triglyceride. The suppository preferably contains from 1 to 95% by weight of the active compound.

The above-mentioned drug compositions suitable for peroral, parenteral, topical or per rectal administration, may be formulated by conventional methods so that after administration to a patient, the active component will be rapidly discharged, gradually discharged or belatedly discharged.

The dose of the compound of the present invention varies depending upon the type of the compound, the administration method, the condition of the patient or the animal to be treated. The optimum dose and the number of administration under a specific condition must be determined by the judgement of a competent doctor. Usually, however, a daily dose to an adult is from about 0.01 g to about 10 g, preferably from about 0.05 g to about 5 g. In the case of the above inhalation method, the dose of the compound of the present invention is preferably from about 0.01 mg to about 100 mg per administration.

Now, specific Formulation Examples of the phospholipase A_2 inhibitor, the anti-inflammatory agent or the anti-pancreatitis agent of the present invention will be given.

FORMULATION EXAMPLE 1 (tablet)		
(1)	Compound No. 30	200 mg
(2)	Lactose	150 mg
(3)	Starch	30 mg
(4)	Magnesium stearate	6 mg

The above composition is tabletted so that the components (1) to (4) constitute one tablet.

FORMULATION EXAMPLE 2 (powder or microgranule)		
(1)	Compound No. 35	200 mg
(2)	Sugar ester (DK ester F-160, manufactured by Daiichi Kogyo)	180 mg
(3)	Surfactant (Dekagreen 1-L, manufactured by Nikko Chemicals)	15 mg
(4)	Light silicic anhydride	25 mg

The component (1) is wet-pulverized in an aqueous solution containing 5% of the component (3). Then, 180 mg of the component (2) is added thereto, and the mixture is freeze-dried. The dried product is pulverized and mixed with the component (4).

The mixture is formed into a powder or microgranule. Such a powder or microgranule may be sealed in a capsule to obtain a capsule drug.

FORMULATION EXAMPLE 3 (hard gelatine capsule)		
(1)	Sodium salt of Compound No. 10	250 mg
(2)	Starch	200 mg
(3)	Magnesium stearate	10 mg

The components (1) to (3) is packed in a hard gelatine capsule to obtain a hard gelatine capsule drug.

FORMULATION EXAMPLE 4 (injection drug)		
(1)	Sodium salt of Compound No. 19	1 g
(2)	Glucose	10 g
(3)	Distilled water for injection	200 ml

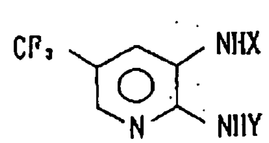
The components (1) to (3) are formulated into an injection drug in accordance with a usual method for preparation of an injection drug.

FORMULATION EXAMPLE 5 (ointment for external skin application)		
(1)	Sodium salt of Compound No. 10	5 g
(2)	White vaseline	25 g
(3)	Stearyl alcohol	22 g
(4)	Propylene glycol	12 g
(5)	Sodium lauryl sulfate	1.5 g
(6)	Ethyl para-hydroxybenzoate	0.025 g
(7)	Propyl para-hydroxybenzoate	0.015 g
(8)	Purified water	100 g

The components (1) to (8) are formulated into an ointment for external skin application by a usual method for preparation of an ointment.

Claims

1. A diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:



(I)

wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y is alkyl, $-CW^3R^6$, $-COCOR^7$, $-NHCOR^7$, $-C(=W^3)W^4R^8$, $-(NH)_mSO_2R^9$, $-(NH)_mSO_2OR^{10}$ or $-(NH)_mSO_2N(R^{11})R^{12}$,

wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded.

2. The diaminotrifluoromethylpyridine derivative or its salt according to Claim 1, wherein said hydrocarbon group for each of R^1, R^6 and R^9 is alkyl, alkenyl or alkynyl; said monocyclic hydrocarbon group for each of R^1, R^6 and R^9 is cycloalkyl, cycloalkenyl or phenyl; said polycyclic hydrocarbon group for each of R^1, R^6 and R^9 is a condensed polycyclic hydrocarbon group such as naphthyl, tetrahydronaphthyl or indanyl, or a bridged polycyclic hydrocarbon group such as adamantyl, noradamantyl, norbornanyl or norbornanonyl; said monocyclic heterocycle group for each of R^1, R^6 and R^9 is pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolinyl, pyrrolidinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, pyrazolinyl, hydantoinyl, oxazolinyl, isoxazolinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, dioxolanyl, dithiolanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, dihydropyridyl, tetrahydropyridyl, piperidinyl, dihydrooxopyridazinyl, tetrahydrooxopyridazinyl, dihyrooxopyrimidinyl, tetrahydrooxopyrimidinyl, piperazinyl, dihydropyranyl, tetrahydropyranyl, dioxanyl, dihydrodithinyl, dithianyl or morphorinyl; said polycyclic heterocycle group for each of R^1, R^6 and R^9 is a condensed polycyclic heterocycle group such as thienothienyl, dihydrocyclopentathienyl, indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzimidazolyl, tetrahydrobenzothienyl, dihydrobenzofuranyl, tetrahydrobenzisoxazolyl, benzodioxolyl, quinolinyl, isoquinolinyl, benzodioxanyl or quinoxalinyl, or a bridged polycyclic heterocycle group such as quinuclidinyl; the substituent for each of the chain hydrocarbon groups which may be substituted for each of R^1, R^6 and R^9, the alkyl which may be substituted and the alkoxy which may be substituted for each of R^2 and R^7, the alkyl which may be substituted, the alkenyl which may be substituted and the alkynyl which may bed substituted for each of R^3, R^8 and R^{10}, the alkyl which may be substituted for each of R^4, R^5, R^{11} and R^{12}, and the alkyl which may be substituted for X^3, is a halogen atom, alkoxy, haloalkoxy, alkylthio, cycloalkyl, cycloalkoxy, cycloalkenyl, cycloalkenyloxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, aryl, aryloxy, arylthio, amino or alkyl-substituted amino; and the substituent for each of the monocyclic hydrocarbon group which may be substituted, the polycyclic hydrocarbon group which may be substituted, the monocyclic heterocyclic group which may be substituted and the polycyclic heterocycle group which may be substituted for each of R^1, R^6 and R^9, the phenyl which may be substituted and the phenoxy which may be substituted for each of R^2 and R^7, the cycloalkyl which may be substituted, the phenyl which may be substituted and the benzyl which may be substituted for each of R^3, R^8 and R^{10}, and the phenyl which may be substituted for X^3, is a halogen atom, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, cycloalkyl, cycloalkoxy, cycloalkenyl, cycloalkenyloxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, aryl, aryloxy, arylthio, amino, alkyl-substituted amino, cyano or nitro.

3. The diaminotrifluoromethylpyridine derivative or its salt according to Claim 1, wherein X is $-CW^1R^1$ or $-C(=W^1)W^2R^3$, and Y is $-SO_2R^9$.

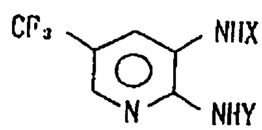
4. The diaminotrifluoromethylpyridine derivative or its salt according to Claim 1, wherein X is $-CW^1R^1$ or $-C(=W^1)W^2R^3$, wherein R^1 is alkyl which may be substituted, alkenyl which may be substituted, cycloalkyl which may be substituted, cycloalkenyl which may be substituted, phenyl which may be substituted, tetrahydronaphthyl which may be substituted, indanyl which may be substituted or thienyl which may be substituted, and R^3 is alkyl which may be substituted, and Y is $-SO_2R^9$, wherein R^9 is alkyl which may be substituted, alkenyl which may be substituted, cycloalkyl which may be substituted,

cycloalkenyl which may be substituted or phenyl which may be substituted.

5. The diaminotrifluoromethylpyridine derivative or its salt according to Claim 1, wherein X is -CW^{1}R^1 or -C(=W^1)W^{2}R^3, wherein R^1 is alkyl, haloalkyl, alkenyl, haloalkenyl, cycloalkyl, halogen-substituted cycloalkyl, phenyl, halogen-substituted phenyl, alkyl- or haloalkyl-substituted phenyl, or alkoxy- or haloalkoxy-substituted phenyl, and R^3 is alkyl or haloalkyl, and Y is -SO$_2$R^9, wherein R^9 is alkyl, haloalkyl, phenyl, halogen-substituted phenyl, alkyl- or haloalkyl-substituted phenyl, or alkoxy- or haloalkoxy-substituted phenyl.

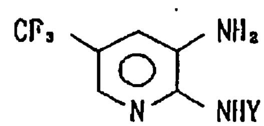
6. The diaminotrifluoromethylpyridine derivative or its salt according to Claim 1, wherein the diaminotrifluoromethylpyridine derivative is at least one derivative selected from the group consisting of N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)cyclohexanecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-5-indanecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-acetoxyacetamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)crotonamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-2-thiophenecarboxamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-trifluoromethylbenzamide, N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-fluorobenzamide, N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-6-(1,2,3,4-tetrahydronaphthalene)carboxamide, N-(2-ethylsulfonylamino-5-trifluoromethyl-3-pyridyl)crotonamide and N-(2-methylsulfonylamino-5-trifluoromethyl-3-pyridyl)-3-(2-thienyl)acrylamide.

7. A process for producing a diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:



(I)

wherein X is -CW^{1}R^1, -COCOR^2, -CW^{1}NHCOR^2, -C(=W^1)W^{2}R^3 or -CW^{1}N(R^4)R^5, and Y is alkyl, -CW^{3}R^6, -COCOR^7, -NHCOR^7, -C(=W^3)W^{4}R^8, -(NH)$_m$SO$_2$R^9, -(NH)$_m$SO$_2$OR^{10} or -(NH)$_m$SO$_2$N(R^{11})R^{12}, wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is -COCF$_2$X^1 wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is -COCF$_2$X^2 wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or -COOX^3 wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded, which comprises reacting a compound of the formula (II):

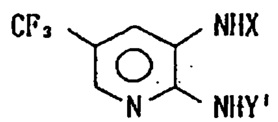


(II)

wherein Y is as defined above, with a compound of the formula Z-CW^{1}R^1 wherein W^1 and R^1 are as defined above, and Z is a halogen atom, a compound of the formula Z-COCOR^2 wherein R^2 and Z are as defined above, a compound of the formula Z-C(=W^1)W^{2}R^3 wherein W^1, W^2, R^3 and Z are as defined above, a compound of the formula Z-CW^{1}N(R^4)R^5 wherein W^1, R^4, R^5 and Z are as defined above, a compound of the formula R^{1}COOH wherein R^1 is as defined above, a compound of the formula (R^{1}CO)-

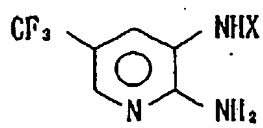
$_2$O wherein R^1 is as defined above or a compound of the formula R^2CONCW^1 wherein W^1 and R^2 are as defined above.

8. A process for producing a diaminotrifluoromethylpyridine derivative of the formula (I-1) or its salt:



(I - 1)

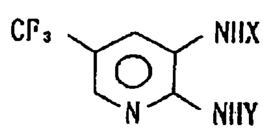
wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y^1 is $-CW^3R^6$, $-COCOR^7$ or $-C(=W^3)W^4R^8$, wherein each of R^1 and R^6, which are independent from each other, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3 and R^8, which are independent from each other, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4 and R^5, which are independent from each other, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded, which comprises reacting a compound of the formula (III):



(III)

wherein X is as defined above, with a compound of the formula $Z-CW^3R^6$ wherein W^3 and R^6 are as defined above, and Z is a halogen atom, a compound of the formula $Z-COCOR^7$ wherein R^7 and Z are as defined above, a compound of the formula $Z-C(=W^3)W^4R^8$ wherein W^3, W^4, R^8 and Z are as defined above, a compound of the formula R^6COOH wherein R^6 is as defined above, or a compound of the formula $(R^6CO)_2O$ wherein R^6 is as defined above.

9. A phospholipase A_2 inhibitor which contains as an active ingredient a diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:

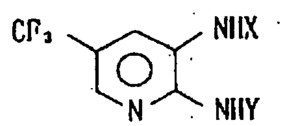


(I)

wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y is alkyl, $-CW^3R^6$, $-COCOR^7$, $-NHCOR^7$, $-C(=W^3)W^4R^8$, $-(NH)_mSO_2R^9$, $-(NH)_mSO_2OR^{10}$ or $-(NH)_mSO_2N(R^{11})R^{12}$, wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are

independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded.

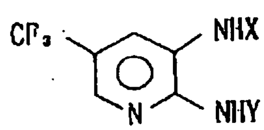
10. An anti-inflammatory agent which contains as an active ingredient a diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:



(I)

wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y is alkyl, $-CW^3R^6$, $-COCOR^7$, $-NHCOR^7$, $-C(=W^3)W^4R^8$, $-(NH)_mSO_2R^9$, $-(NH)_mSO_2OR^{10}$ or $-(NH)_mSO_2N(R^{11})R^{12}$, wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded.

11. An anti-pancreatitis agent which contains as an active ingredient a diaminotrifluoromethylpyridine derivative of the formula (I) or its salt:

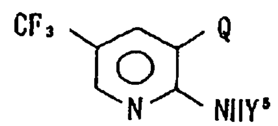


(I)

wherein X is $-CW^1R^1$, $-COCOR^2$, $-CW^1NHCOR^2$, $-C(=W^1)W^2R^3$ or $-CW^1N(R^4)R^5$, and Y is alkyl, $-CW^3R^6$, $-COCOR^7$, $-NHCOR^7$, $-C(=W^3)W^4R^8$, $-(NH)_mSO_2R^9$ $-(NH)_mSO_2OR^{10}$ or $-(NH)_mSO_2N(R^{11})R^{12}$ wherein each of R^1, R^6 and R^9, which are independent from one another, is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, each of R^2 and R^7, which are independent from each other, is alkyl which may be substituted, alkoxy which may be substituted, phenyl which may be substituted or phenoxy which may be substituted, each of R^3, R^8 and R^{10}, which are independent from one another, is alkyl which may be substituted, alkenyl which may be substituted,

alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, each of R^4, R^5, R^{11} and R^{12}, which are independent from one another, is alkyl which may be substituted, each of W^1, W^2, W^3 and W^4, which are independent from one another, is an oxygen atom or a sulfur atom, and m is 0 or 1, provided that a combination wherein one of X and Y is $-COCF_2X^1$ wherein X^1 is a hydrogen atom, a halogen atom, alkyl or haloalkyl, and the other is $-COCF_2X^2$ wherein X^2 is a hydrogen atom, a halogen atom, alkyl, haloalkyl or alkylcarbonyl, or $-COOX^3$ wherein X^3 is alkyl which may be substituted or phenyl which may be substituted, is excluded.

12. A trifluoromethylpyridine derivative of the formula (VIII):



(VIII)

wherein Q is a hydrogen atom, nitro or amino, and Y^5 is $-(NH)_mSO_2R^9$ wherein R^9 is a chain hydrocarbon group which may be substituted, a monocyclic hydrocarbon group which may be substituted, a polycyclic hydrocarbon group which may be substituted, a monocyclic heterocycle group which may be substituted or a polycyclic heterocycle group which may be substituted, and m is 0 or 1, $-(NH)_mSO_2OR^{10}$ wherein R^{10} is alkyl which may be substituted, alkenyl which may be substituted, alkynyl which may be substituted, cycloalkyl which may be substituted, phenyl which may be substituted or benzyl which may be substituted, and m is as defined above, or $-(NH)_mSO_2N(R^{11})R^{12}$ wherein each of R^{11} and R^{12} is alkyl which may be substituted, and m is as defined above, provided that when Q is a hydrogen atom and m is 0, R^9 is other than naphthyl or phenyl which may be substituted.